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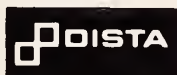
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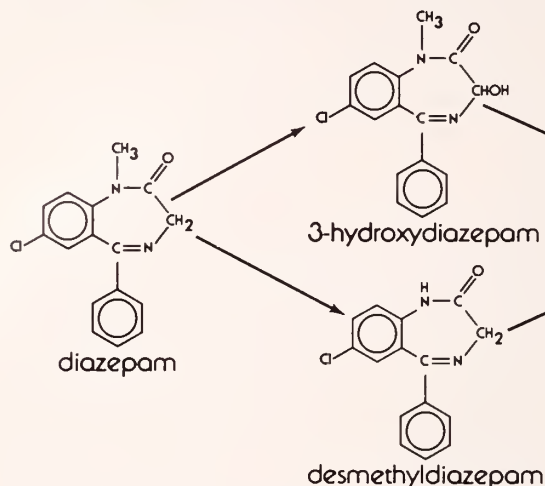
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# The Journal of the Maine Medical Association

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Number 1

## The Need For Family Physicians in Maine

A. DEWEY RICHARDS, M.D. and MARTHA P. GYGER, A.S.

### INTRODUCTION

The need for a large number of additional primary care physicians in the State of Maine is obvious to most persons rendering service to patients in this area. Studies of need for health care services have amply confirmed this.<sup>1,2</sup> In spite of this, it has been stated nationally that Maine has reached the "goal" of a family physician to population ratio of 1:2,500 suggested by the American Academy of Family Physicians.<sup>3</sup> This statement has been misconstrued to mean that no further primary care physicians are needed in Maine.

Schonfeld's careful calculations document a need for 133 primary care physicians to give 100,000 persons good care in the field of internal medicine and pediatrics. His figures do not include obstetrics, mental problems, and routine physicals, so the actual need for primary care physicians is greater than his calculations of one for 752 persons.

Combining the AAFP recommendations and Dr. Schonfeld's data, Maine's 1,000,000 people need 1,330 primary care physicians, at least one-third of which should be family physicians.<sup>4</sup> This number is more than three times the actual number of full-time family physician equivalents recently calculated to be 412 in a recent study by Dr. Robert True, and is actually very close to the total number of MDs and DOs now practicing in the State.

Other articles quote maldistribution and improper training as the major problems.<sup>5</sup> Almost all recognize a need for more family physicians. The AMA statistics show 112,000 general practitioners in 1931 and 52,330 in 1970. In 1945, there were 69 counties without a doctor compared to 138 counties without a doctor in 1973. The difficulty experienced by patients in finding a family physician in urban

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TABLE 1

	QUESTIONNAIRE RESPONSE		
	Total Sent	Total Returned	Percentage
MMA & ME Physicians	1,045	510	48.80%
ME AAFP Members	98	59	60.20%
Osteopaths	186	55	30.05%
TOTALS	1,326	624	47.06%

TABLE 2

AAFP MAINE CHAPTER SURVEY	
1. Are more F.P.s needed in your area now?	
YES: 45 ( 76.27%)	NO: 14 (23.73%)
2. Do you need an associate or partner?	
YES: 15 ( 28.30%)	NO: 38 (71.70%)
3. Would you help another F.P. get started?	
YES: 50 (100.00%)	NO: 0 (—)
4. In your town?	
YES: 43 ( 81.13%)	NO: 10 (18.87%)
5. In a nearby town?	
YES: 43 ( 89.58%)	NO: 5 (10.42%)
6. By referring him patients?	
YES: 36 (73.47%)	NO: 13 (26.53%)
7. By crosscovering him?	
YES: 30 (62.50%)	NO: 18 (37.50%)
8. By guaranteeing him an income?	
YES: 4 ( 8.89%)	NO: 41 (91.11%)

areas of Maine is as great as in the rural areas of the State. In spite of some general statistics and generally accepted opinions, there was no current data available to accurately describe the magnitude of the need for physicians in Maine.

The purpose of this study was to assemble and collate meaningful data to describe the current need for physicians in the State as assessed by physicians and osteopaths presently practicing in Maine communities.

The method selected was a postal card survey. Postal card questionnaires were sent to Maine physicians (primarily the members of the Maine Med-

TABLE 3

MMA MEMBERS/MAINE PHYSICIANS & OSTEOPATHS SURVEY		
1. Are doctors needed in your area now?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 329 (70.45%)	38 (73.08%)	
NO: 138 (29.55%)	14 (26.92%)	
2. Is there need for more Family Physicians?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 353 (76.91%)	38 (73.08%)	
NO: 106 (23.09%)	14 (26.92%)	
3. Is there need for more Internists?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 216 (48.32%)	17 (34.69%)	
NO: 231 (51.68%)	32 (65.31%)	
4. Is there need for more Pediatricians?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 185 (43.53%)	26 (56.52%)	
NO: 240 (56.47%)	20 (43.48%)	
5. Do you need an associate or partner?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 101 (22.20%)	14 (27.45%)	
NO: 354 (77.80%)	37 (72.55%)	
6. Would you help a doctor get started?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 345 (83.54%)	45 (88.24%)	
NO: 68 (16.46%)	6 (11.76%)	
7. In your town?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 324 (80.00%)	35 (74.47%)	
NO: 81 (20.00%)	12 (25.53%)	
8. In a nearby town?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 262 (73.18%)	38 (82.61%)	
NO: 96 (26.82%)	8 (17.39%)	
9. By referring him patients?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: (82.13%)	41 (87.23%)	
NO: 72 (17.87%)	6 (12.77%)	
10. By crosscovering him?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 154 (40.96%)	30 (65.22%)	
NO: 222 (59.04%)	16 (34.78%)	
11. By guaranteeing him an income?		
<i>MMA &amp; ME Physicians</i>	<i>Osteopaths</i>	
YES: 44 (12.83%)	4 (10.53%)	
NO: 299 (87.17%)	34 (89.47%)	

ical Association), the State of Maine Academy of Family Physicians, and to all osteopaths practicing in the State. Selection was made to insure that only one card went to a physician, although he might have been represented by more than one of the groups. Two sets of questions were used. The first was sent to the members of the State of Maine Academy of Family Physicians. The second was sent to the members of the MMA, to nonmember Maine physicians, and to the practicing osteopaths in the State.

Table 1 shows the response to the questionnaires; the high-percentage return indicates the level of interest.

Table 2 shows the questionnaire sent to all members of the State of Maine Academy of Family Physicians. Table 3 shows the questionnaire sent to the members of the Maine Medical Association, to nonmember Maine physicians, and to the osteopaths.

At the bottom of each postal card was a request for the physician to list those towns which need and

TABLE 4

PHYSICIAN NEED IN MAINE COMMUNITIES**			
Albion	1	Fort Kent	2
Anson	1	Freedom	1
Ashland	4	Freeport	7
Auburn	13	Friendship	2
Augusta*	20	Gardiner	6
Bangor*	44	Gorham	1
Bar Mills	1	Gray	6
Bath*	6	Greene	1
Belfast*	4	Greenville*	6
Belgrade	3	Guilford	2
Berwick	1	Hallowell	1
Bethel	1	Hampden	1
Biddeford*	8	Hampden Highlands*	1
Bingham	10	Harpswell	2
Blue Hill	1	Harrington	1
Boothbay Harbor	3	Harrison	2
Bowdoinham	1	Hartland	2
Brewer	2	Hiram	1
Brunswick	7	Hollis Center	1
Bucksport*	5	Houlton	6
Buxton	2	Howland	1
Calais	6	Jackman	3
Camden	5	Jefferson	1
Canton	1	Jonesport	2
Cape Elizabeth	3	Kennebunk*	4
Cape Neddick	1	Kennebunkport	2
Caribou*	3	Kezar Falls	7
Castine	1	Kingfield	7
Corinna	1	Kittery	1
Cumberland Center	3	Leeds	2
Deer Isle	1	Lewiston*	40
Dexter	6	Limerick	5
Dixfield	2	Limington	1
Dixmont	1	Lincoln	7
Dover-Foxcroft	3	Lisbon	2
Eagle Lake	1	Lisbon Falls	11
East Corinth	3	Livermore Falls	4
East Machias	1	Lubec	1
East Millinocket*	5	Madawaska	4
Easton	1	Madison	11
Eastport	4	Mattawamkeag	1
Eliot	2	Mechanic Falls	8
Ellsworth	3	Medway	1
Falmouth	5	Mexico	1
Farmington*	12	Milbridge*	2
Millinocket*	12	Sanford*	4
Milo	9	Scarborough*	5
Monmouth	1	Searsport	1
Moody	1	Sebago Lake	1
Mount Desert	1	Sherman	1
Newburgh	1	Sherman Mills	1
New Gloucester	2	Skowhegan	4
Newcastle	1	South Berwick	1
Newport	4	South Portland	4
Norridgewock	1	South Windham	2
North Anson	1	Southwest Harbor	3
North Berwick	2	Springvale	1
North Windham	1	Steep Falls	1
North Yarmouth	1	Stillwater	1
Northeast Harbor	1	Strong	1
Norway	2	Sullivan	1
Oak Hill	1	Sydney	1
Oakland	1	Thomaston	4
Ogunquit	1	Topsham	1
Old Orchard Beach	1	Turner	1
Old Town	11	Union	2
Orono*	9	Unity	1
Otisfield	1	Van Buren	2
Oxford	1	Vassalboro	3
Patten	1	Waldoboro	6
Pembroke	1	Warren	3
Pineland	1	Washburn	2

Pittsfield	3	Waterboro	2
Pittston	1	Waterford	4
Pleasant Point	1	Waterville*	22
Portland*	47	Wells	2
Presque Isle*	8	Westbrook	7
Rangeley	4	Wilton	1
Raymond	1	Windham	1
Richmond	14	Winthrop	4
Rockland	7	Wiscasset	6
Rockport	2	Woodland*	3
Rumford*	12	Yarmouth	3
Saco*	8	York*	1
Saint George	1		

\*\* Figures represent number of practicing physicians who feel there is a need for at least one physician in this community.

\*At least one physician in this community has expressed willingness to guarantee an income to a new physician to practice in his area.

TABLE 5

PHYSICIANS WILLING TO GUARANTEE INCOME	
<i>AAFP Members:</i>	Kennebunk*
York*	Lewiston*****
Woodland*	Milbridge*
Farmington**	Millinocket**
<i>MMA &amp; ME Physicians:</i>	Orono*
Augusta***	Portland*****
Bangor***	Presque Isle*
Bath**	Rumford**
Belfast*	Saco*
Biddeford**	Sanford*
Bucksport*	Waterville****
Caribou*	<i>Osteopaths:</i>
East Millinocket*	Bangor**
Farmington*	Portland*
Greenville**	Scarborough*
Hampden Highlands*	

\*Asterisks represent number of physicians in this community who have expressed a willingness to guarantee an income to a new physician to practice in his area.

could support a family physician. In Table 4 the number beside the name of the town indicates the number of physicians who feel that at least one additional physician is needed in that town. An asterisk indicates that a physician in that community is willing to guarantee an income to a new physician practicing in his area.

Table 5 is the list of communities in which a physician has expressed a willingness to guarantee an income to a new physician. The asterisks after the towns indicate the number of physicians who have expressed a willingness to guarantee an income to a physician to practice in this town.

Table 6 is a list of communities needing physicians as seen by the responding members of the State of Maine Academy of Family Physicians, with the numbers representing the number of physicians who feel there is the need for at least one additional physician in the community. A similar list as described by the osteopaths is Table 7. The list as described by the Maine Medical Association members and nonmember Maine physicians is Table 8.

TABLE 6

PHYSICIAN NEED IN MAINE COMMUNITIES AS FELT BY MAINE AAFP CHAPTER MEMBERS*			
Augusta	1	Leeds	1
Ashland	1	Lewiston	3
Auburn	4	Limerick	2
Bath	1	Lisbon Falls	5
Belfast	1	Livermore Falls	1
Bingham	1	Madawaska	1
Blue Hill	1	Madison	1
Bowdoinham	1	Mechanic Falls	1
Brunswick	2	Milo	3
Calais	3	Moody	1
Camden	1	Newcastle	1
Cape Neddick	1	New Gloucester	1
Corinna	1	Newport	1
Deer Isle	1	North Berwick	2
Dexter	2	Ogunquit	1
Dover-Foxcroft	1	Old Town	1
Eastport	2	Pittsfield	1
Falmouth	2	Portland	7
Farmington	3	Rangeley	1
Fort Kent	1	Richmond	2
Freeport	2	Scarborough	1
Gardiner	1	South Windham	1
Gray	3	Waldoboro	1
Greenville	2	Waterford	2
Guilford	1	Westbrook	3
Hartland	1	Winthrop	1
Houlton	2	Wiscasset	2
Jackman	1	Woodland	2
Kingfield	2	Yarmouth	2

\*Figures represent number of practicing physicians who feel there is a need for at least one physician in this community.

TABLE 7

PHYSICIAN NEED IN MAINE COMMUNITIES AS FELT BY MAINE OSTEOPATHS*			
Auburn	1	Milbridge	1
Bangor	2	Millinocket	2
Bar Mills	1	Milo	1
Belgrade	1	New Gloucester	1
Bethel	1	North Anson	1
Bingham	1	North Yarmouth	1
Camden	2	Orono	1
Canton	1	Owls Head	1
Cape Elizabeth	1	Portland	6
Dexter	1	Presque Isle	2
Dixfield	1	Rockland	1
Eliot	1	Saco	1
Falmouth	1	Saint George	1
Farmington	1	Scarborough	1
Freeport	3	Sherman Mills	1
Gray	2	South Portland	2
Greenville	1	South Windham	1
Harrington	1	Stillwater	1
Hiram	1	Strong	1
Hollis	1	Thomaston	2
Jackman	1	Union	1
Kezar Falls	3	Unity	1
Kingfield	1	Vassalboro	1
Kittery	1	Waldoboro	2
Lewiston	1	Warren	1
Lincoln	1	Waterville	2
Mattawamkeag	1	Westbrook	1
Mechanic Falls	3	Wiscasset	2

\*Figures represent number of practicing physicians who feel there is a need for at least one physician in this community.

TABLE 8

## PHYSICIAN NEED IN MAINE COMMUNITIES AS FELT BY MMA MEMBERS AND MAINE PHYSICIANS

Albion	1	Hallowell	1	Patten	1
Anson	1	Hampden	1	Pembroke	1
Ashland	3	Hampden Highlands	1	Pineland	1
Auburn	8	Harpswell	2	Pittsfield	2
Augusta	19	Harrison	2	Portland	34
Bangor	42	Hartland	1	Presque Isle	6
Bath	5	Houlton	4	Rangeley	3
Belfast	3	Howland	1	Raymond	1
Belgrade	2	Jackman	1	Richmond	12
Berwick	1	Jefferson	1	Rockland	6
Biddeford	8	Jonesport	2	Rockport	2
Bingham	8	Kennebunk	4	Rumford	12
Boothbay Harbor	3	Kennebunkport	2	Saco	7
Brewer	2	Kezar Falls	4	Pleasant Point	1
Brunswick	5	Kingfield	4	Pittston	1
Bucksport	5	Lewiston	36	Sanford	4
Buxton	2	Limerick	3	Scarborough	3
Calais	3	Limington	1	Searsport	1
Camden	3	Lincoln	6	Sebago Lake	1
Cape Elizabeth	2	Lisbon	2	Sherman	1
Caribou	3	Lisbon Falls	6	Skowhegan	4
Castine	1	Livermore Falls	3	South Berwick	1
Cumberland Center	3	Leeds	1	South Portland	2
Dexter	3	Lubec	1	Southwest Harbor	3
Dixfield	1	Madawaska	3	Springvale	1
Dixmont	1	Madison	10	Steep Falls	1
Dover-Foxcroft	2	Mechanic Falls	4	Sullivan	1
Eagle Lake	1	Medway	1	Sydney	1
East Corinth	3	Mexico	1	Thomaston	2
East Machias	1	Milbridge	1	Topsham	1
East Millinocket	5	Millinocket	10	Turner	1
Easton	1	Milo	5	Union	2
Eastport	2	Monmouth	1	Van Buren	2
Eliot	1	Mount Desert	1	Vassalboro	2
Ellsworth	3	Newport	3	Waldoboro	3
Falmouth	2	Norridgewock	1	Warren	2
Farmington	8	North Windham	1	Washburn	2
Fort Kent	1	Northeast Harbor	1	Waterford	2
Freedom	1	Norway	2	Waterville	20
Freeport	2	Oakland	1	Wells	2
Friendship	2	Old Orchard Beach	1	Westbrook	3
Gardiner	5	Old Town	10	Wilton	3
Gorham	1	Newburgh	1	Winthrop	3
Gray	1	Oak Hill	1	Wiscasset	2
Greene	1	Orono	8	Woodland	1
Greenville	4	Orrington	1	Windham	1
Guilford	1	Otisfield	1	Yarmouth	1
		Oxford	1	York	1

\*Figures represent number of practicing physicians who feel there is a need for at least one physician in this community.

## DISCUSSION

Two separate questionnaires were used to gain comparative but separate data. The need for family physicians as seen by the State of Maine Academy of Family Physicians shows more than three-fourths of those responding indicating a need for more family physicians in their area now. An almost identical number of the MMA members and non-members and osteopaths indicated the same opinion. The need for internists and pediatricians is seen as significantly less.

The indicated willingness to assist another physician get started with multiple types of support is emphasized by the 52 respondents who would go as far as to guarantee an income to a starting physi-

cian. The arms of the physicians of Maine are certainly wide open to any family physician seeking a place to practice.

## SUMMARY

The survey demonstrates that a high percentage of the physicians responding declare a need for more family physicians in the State. The geographic distribution of the need covers the entire State. The largest cities would also be considered critical shortage areas by this survey. The data verifies the shortage of family physicians throughout the State. It makes abundantly apparent the attitude of the physicians of the State in their eagerness to en-

*Continued on Page 7*

# Subtotal Pancreatectomy for Hyperlipidemia Induced Acute Necrotizing Pancreatitis

H. CLEMENT JURGELEIT, M.D.\*

Acute necrotizing (hemorrhagic) pancreatitis is frequently a lethal disease. Although this fulminant form of the disease comprises under 5% of patients with acute pancreatitis, its mortality rate is generally regarded to be over 90%.<sup>1,2</sup> In recent years, surgical intervention has been advocated in such patients with severe pancreatitis who are unresponsive to maximal medical therapy in an attempt to reduce the mortality.<sup>3-11</sup> The basic operative plan has been to provide external drainage for the highly toxic and destructive pancreatic exudates; debridement with pancreatic resection has been described.

This report describes a young female patient with hyperlipidemia on oral contraceptives who developed acute necrotizing pancreatitis in which tissue destruction was so extensive that debridement of as much devitalized tissue as possible was deemed indicated, involving a resection of a major part of the tail and body of the pancreas.

## CASE REPORT

A. H. is a 24-year-old white female who was admitted on an urgent basis to Eastern Maine Medical Center on March 13, 1976 with generalized progressive abdominal pain, nausea, vomiting and fever of twelve hours' duration. There was no prior history of gastrointestinal symptoms nor of any significant alcohol consumption. She had been taking oral contraceptive medication for about six weeks. On examination she was acutely ill with a temperature of 102 R., a pulse of 100 and generalized abdominal pain and tenderness, questionably more in the epigastrium and right upper quadrant. WBC was 12,500/mm<sup>3</sup>; serum amylase was 45 u. (normal up to 160 u.). Initial treatment was directed toward possible acute cholecystitis with antibiotics and nasogastric intubation. Over the next 48 to 72 hours, she became progressively more toxic. Abdominal pain and distention increased with more localizing signs in the hypogastrium. Liver function tests were normal, WBC 12,000 to 13,000/mm<sup>3</sup>; serum amylase rose to a maximum of 205 u. on 3/15; serum lipase was normal. Significantly severe hypocalcemia, hypoalbuminemia and hypercholesterolemia ensued with a serum calcium of 5.2 mg.% on 3/14 and 4.7 mg.% on 3/15. Serial abdominal films showed progressive loss of soft tissue lines in the retroperitoneum. An intravenous cholangiogram was normal on 3/15. The patient became more dyspneic and toxic with increasing signs of peritoneal irritation. Surgical exploration was carried out on 3/16/76 with a presumptive diagnosis of pelvic-abdominal sepsis. Massive retroperitoneal hemorrhagic necrosis extended from the retrogastric and subhepatic regions to retrocecal and retrocolic regions of the pelvis, resembling a "sea of thick mud;" necrosis extended into the subserosal planes of the posterior (mesenteric) side of the right, transverse and left colon (Figure 1). The pancreas was "mush" with only a central core of glandular integrity remaining.



Fig. 1. Intraoperative view from the cephalad to caudad direction. The right colon is reflected medially. The massive retroperitoneal hemorrhagic necrosis extending into the subserosal planes of the bowel wall is visualized.

There was hemorrhagic ascitic fluid with an amylase of 621 u.; amylase of the retroperitoneal "mud" was 2907 u. A colotomy confirmed the viability of the colon. Debridement of copious amounts of the necrotic tissue was carried out. Splenectomy and an 80% distal pancreatectomy was performed in an attempt to remove as much devitalized tissue as feasible. A gastrostomy was done for long-term decompression, sump drains were placed in the lesser sac (area of pancreatic bed) and Foramen of Winslow, and multiple tissue drains were placed in various other areas of involvement (subhepatic, right gutter, left subphrenic, left gutter, pelvis). Postoperative respiratory failure required assisted ventilation for several days. Intravenous hyperalimentation was instituted to a level of 3000 to 4000 calories a day and the sump drains were intermittently irrigated with saline. Antibiotic coverage was given as well as large amounts of albumin and calcium. The initial operative cultures were negative but later cultures from drain sites yielded *Bacteroides*, *Enterococcus* and *Staphylococcus epidermidis* consistently throughout the hospital stay (except for the addition of *E. coli* in the third month). Rapid initial improvement was followed by recurrent sepsis. Re-exploration on 4/3 revealed both right and left retroperitoneal abscesses (right, retrocolic; and left, caudal to pancreatic bed). Waterman type sump drains<sup>6</sup> as well as other tissue drains were placed; they were continuously irrigated with lactated ringers solution for fourteen days. Postoperative hyperalimentation and antibiotics were continued. By 4/15 she was afebrile with some return of bowel function and oral feeding was started. The expected diabetic state, a sequel to the pancreatectomy and aggravated by the sepsis and high level of hyperalimentation, required up to fifty units of crystalline insulin every four hours. The pancreatic drain continued to exude particles of necrotic tissue and the irrigant was high in amylase content. Signs of further recurrent sepsis were evident by mid-May with fever and leukocytosis, and on 5/19 left flank exploration was performed with drainage of septic necrotic tissue in the left retroperitoneum (left retrocolic area). Sump drainage and irrigations again for ten days of both left flank and pancreatic areas was followed by rapid

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improvement with decreasing sump drainage, defervescence and progression to a full regular diet and activity. She was discharged on 6/7/76, the 86th hospital day. By the time of discharge, the fasting and two-hour post-prandial blood sugars were normal on a regular unrestricted diet. However, at two months follow-up, when feeling well with full activity and on an unrestricted diet, a glucose tolerance test was decidedly abnormal with a fasting glucose of 133 mg%, 1 hr 255 mg%, 2 hr 271 mg% and 3 hr 172 mg%. Furthermore, at that time the serum cholesterol was 828 mg% and triglycerides 1190 mg%, both markedly elevated; a lipoprotein electrophoresis was consistent with a Type V Hyperlipidemia (Fredrickson classification).

## DISCUSSION

In 1968, Bolooki and Gliedman<sup>12</sup> reported some improvement in patients with severe fulminant pancreatitis using peritoneal dialysis. Waterman et al<sup>6</sup> in the same year reported a survival of nine out of ten patients following drainage of the lesser sac with a sump drain of two red rubber catheters surrounded by a fenestrated Penrose drain. In 1970, Lawson et al<sup>3</sup> at the Massachusetts General Hospital proposed the "MGH operation," i.e., cholecystostomy, gastrostomy, feeding jejunostomy and sump drainage of the lesser sac and Foramen of Winslow peripancreatic areas. The rationale was to decompress the biliary tree, which may be the possible etiology or contributing factor to the disease, drain the stomach to reduce pancreatic stimulation by secretin and gastrin — decompression may need to be prolonged to avoid recurrent attacks — and provide a means of providing adequate nutrition to the patient during the period of gastroduodenal de-functionalization. In 1973, Rosato et al<sup>4</sup> reported a lavage technique via the above described sumps, and seven of eight patients survived. Warshaw et al,<sup>5</sup> in 1974, compiled a series of 38 patients in various stages and degrees of pancreatitis in whom the "MGH operation" was done, and seven of the eleven with acute fulminant disease states survived. Drainage done for late sequelae of acute pancreatitis (sepsis, pseudocyst), was also of benefit with twelve of eighteen surviving. No benefit was derived from operation on patients with lesser degrees of pancreatitis.

Most patients with acute pancreatitis do not belong on the operating table. It is the catastrophically ill, rapidly deteriorating patient with borderline shock and respiratory failure that often responds dramatically to surgical drainage and decompression. As discussed by Warshaw,<sup>5</sup> the mechanism for improvement is in providing a route of egress of the severely toxic pancreatic enzymes and products of digestion. Secondary complications are frequent with recurrent sepsis the major problem — a 42% incidence of abscesses in the series reported, vs. a 4 to 5% incidence in pancreatitis overall. Fistulae and pseudocyst are other less frequent problems. In his series, sepsis was the cause of death in most of the patients (ten of thirteen) emphasizing that pancreatic sepsis undrained is a deadly form of intra-abdominal sepsis. Five of the deaths in that series were deemed preventable in retrospect, had recur-

rent sepsis been recognized and drained.

Reports are few regarding actual pancreatic resection for this disease. Watts, in 1963,<sup>10</sup> in England, reported a total pancreatectomy and Khedroo and Casella, in 1966,<sup>11</sup> described subtotal resection of necrotic pancreas for fulminant pancreatitis. Norton and Eiseman<sup>7</sup> reported four cases of 65 to 85% distal pancreatectomy with three survivors. Resection of as much necrotic pancreas as possible may be considered merely an extension of debridement and drainage — when necrosis and devitalization are so severe that removal of the diseased and destroyed gland with its exuding toxic products seems reasonable and desirable. The most extensive experience with resection for acute necrotizing pancreatitis is that of Hollender et al<sup>8</sup> with a survival rate of about 65%. Finally, White and Heimbach<sup>9</sup> recently have proposed an initial drainage procedure with gastric and biliary decompression and parenteral hyperalimentation, followed at a later date by sequestrectomy of remaining necrotic pancreas should this become necessary — only 50% of their series of patients required such a second procedure. Overall survival was 80%.

The etiology of the pancreatitis in the present case seems to be on the basis of a previously undiagnosed pre-existing hyperlipidemia. Hyperlipidemia, in particular, Type I and V of the Fredrickson classification, is a well described predisposing factor in the development of acute pancreatitis.<sup>13</sup> Despite intensive study, the mechanism by which this occurs remains to be defined. There is fairly good evidence, however, that a sudden and marked elevation in serum triglycerides predisposes to a bout of pancreatitis; and that control of the triglyceride level with a low fat diet considerably reduces the frequency of acute pancreatitis in these patients.<sup>13</sup>

Serum lipids are known to be increased in women taking oral contraceptive steroids; it appears to be the estrogen and not the progestagen content that is responsible for the elevated level.<sup>14</sup> Davidoff et al<sup>15</sup> describe two patients with a Type IV Hyperlipidemia who developed acute pancreatitis while on oral contraceptive medication; each was associated with striking elevations in serum triglycerides which dramatically dropped on recovery from the pancreatitis and discontinuance of the drug. The rise in serum lipids induced by oral contraceptive agents in patients with a pre-existing hyperlipidemia is much more marked than in those with a normal lipid pattern; the mechanism of this disproportionate increase is not known. Caution should be exercised in the use of oral contraceptive drugs and other estrogen compounds in women with hyperlipidemia, particularly those with Type I, IV, and V.

It is important to emphasize that serum amylase and lipase and urinary amylase levels are frequently normal in hyperlipidemic patients with pancreatitis (as was the situation with this patient). Severe abdominal pain accompanied by grossly lactescent

serum with normal amylase and lipase should alert one to the possible diagnosis of hyperlipidemia induced acute pancreatitis; this is especially so in the young female patient on oral contraceptives where acute biliary tract disease may seem more likely. Severe hypocalcemia, hypoalbuminemia, the dramatic loss of soft tissue shadows on X-ray and the impending respiratory failure may be signs of the more fulminant form of the disease. Edmondson et al<sup>16</sup> have noted that a serum calcium below 7.0 mg% is a particularly poor prognostic sign in this disease.

This patient underwent a modified and extended "MGH operation" of decompression and drainage with pancreatic resection and postoperative sump lavage. Since the preoperative intravenous cholangiogram was normal and intravenous hyperalimentation was used for nutrition, cholecystostomy and a feeding jejunostomy were not deemed necessary. The metabolic support with hyperalimentation, prolonged sump drainage and lavage, and re-operation for recurrent sepsis were felt to be the key features of management. And as noted by Warshaw et al,<sup>5</sup> there should be little hesitation to re-operate for recurrent sepsis which is almost an expected sequela. The late development of diabetes mellitus is not surprising. Although the fasting and two-hour postprandial serum glucose levels were normal on discharge in June, a frank diabetic state developed on an unrestricted home diet and activity. It is hoped dietary management will afford adequate control without need of exogenous insulin. It is further anticipated that strict control of dietary fat intake will control the hyperlipidemic condition and thereby greatly reduce the chances for a recurrent bout of pancreatitis. In view of the possible etiologic role of oral contraceptives, other forms of contraception have been strongly advised.

#### SUMMARY

A case of acute necrotizing pancreatitis asso-

ciated with Type V Hyperlipidemia is presented. The possible etiologic role of oral contraceptives is discussed. Subtotal pancreatic resection with sump drainage was done, and two further explorations were required for recurrent sepsis. The clinical features and surgical management of this fulminant and often lethal form of pancreatitis are discussed. Since recurrent sepsis is frequent, early re-operation for drainage is emphasized.

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courage new physicians. The listed towns should be useful to a physician seeking a place in Maine to practice.

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# Coronary Arteriography at a Regional Medical Center

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Coronary arteriography, a technique developed almost 20 years ago, is widely used in the evaluation of patients who have, or are suspected of having, ischemic heart disease. Initially, this procedure was performed only at large medical centers but now, due to the large number of patients who need the study, this procedure is being performed at regional and community hospitals. The reported risk of complication of coronary arteriography varies widely in the studies published.<sup>1-10</sup> Large surveys cite mortality rates from 0.1-8% and suggest that this variation is related, at least in part, to the case load.<sup>1,2</sup> Reports from two non-university affiliated community hospitals with mortality rates of 0.16% and 0.43% for coronary arteriography show that this procedure is being performed in community hospitals at an acceptably low risk.<sup>11,12</sup> The purpose of this report is to relate our experience with the first 250 consecutive patients studied by coronary arteriography at the Eastern Maine Medical Center, a non-university affiliated hospital, with case load smaller than most university centers.

## METHODS

During the first 29 months of operation, selective coronary arteriography was performed on 250 patients in our hospital. Two hundred and thirty-one patients were studied by the percutaneous transfemoral technique using preformed polyethylene catheters (Cook series) and 19 patients by the retrograde brachial arteriotomy technique with standard woven dacron Sones catheters (USCI). In most instances, ischemic heart disease was suspected or documented clinically and studies were performed to determine the proper therapeutic approach. Forty-four patients had selective coronary arteriography in conjunction with right and left heart catheterization for the study of congenital, valvular or myocardial disease. The patients were admitted 12 to 24 hours prior to study, were fasting and premedicated with diazepam 10 mg. orally. Studies on all patients were performed by the same two cardiologists. The primary operator placed the catheter and directed the study. The second cardiologist operated the stop clock/syringe manifold, injected small amounts of contrast to assist with exact and rapid catheter replacement and performed the injections. All studies were viewed on videotape and the patient position and number of injections were altered as necessary to obtain the best demonstra-

tion of the anatomy. The study of each vessel was reviewed for accuracy and completeness prior to proceeding to the next part of the study. Right heart catheterization and temporary pacemaker insertions were not performed unless specifically indicated. Nitroglycerin and atropine were not routinely used. When the transfemoral technique was used, 40 mg. of heparin sodium was given intra-arterially through the first catheter and 20 mg. of protamine sulfate was given intravenously before the last catheter was removed (With the brachial arteriotomy technique, 20 mg. of dilute heparin sodium was injected distal to the arteriotomy at the beginning and end of the procedure). The heparin coated guide wires were completely withdrawn before the catheter was advanced around the aortic arch and the assistant injected repeated small amounts of contrast during the approach and final positioning of the catheter tip. The left coronary artery was studied first in four views which demonstrated the anatomy to the best advantage — usually 10 degrees and 30 degrees RAO, 45-60 degrees LAO and lateral positions. Occasionally these views were supplemented by a shallow RAO or LAO view with 30 degrees cranio-caudal angulation obtained by elevating the patient's trunk on a wooden wedge. Left coronary cusp injections in a shallow RAO position were used prior to selective catheterization when left main coronary artery stenosis was suspected and, if present, injections were kept to a minimum. The right coronary artery was studied in three positions which included lateral, 60 degrees LAO and 30 degrees RAO. Saphenous vein grafts were selectively injected using the performed right coronary artery catheter (Judkins). Left ventriculography in the RAO position was performed after the coronary arteriography with a pigtail catheter using a single injection of 40 to 50 c.c. of Renografin®-76 at 15 c.c. per second. Occasionally this view was supplemented with a second ventriculogram in the LAO position. Aortic and left ventricular pressures were measured before and after left ventriculography. The presence of a distal arterial pulse was confirmed prior to removal of the catheter. Record was made of the fluoroscopy time, the length of time the catheter was in the arterial system ("catheter in time") and the amount of contrast material used. The patients were observed for 24 hours following the procedure and note was made of any complications which occurred during this time. Blood samples for total CPK activity determinations were obtained 24 hours after catheterization.

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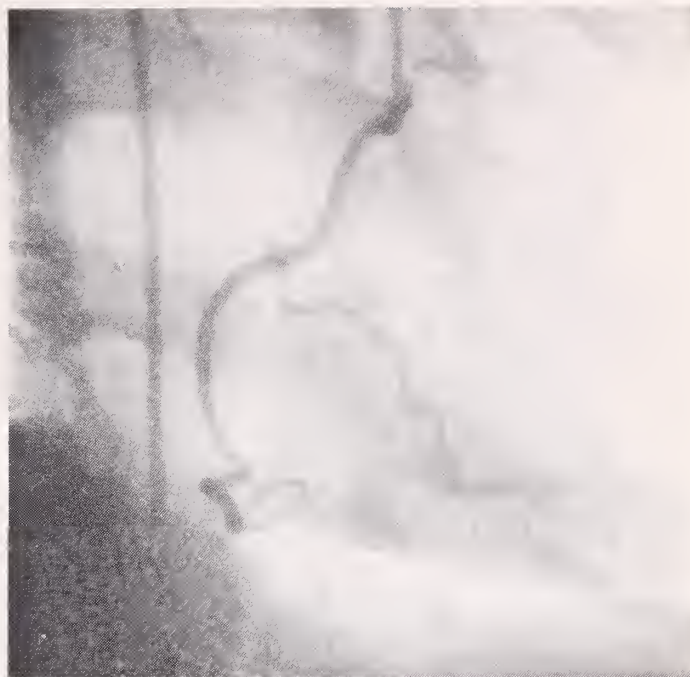
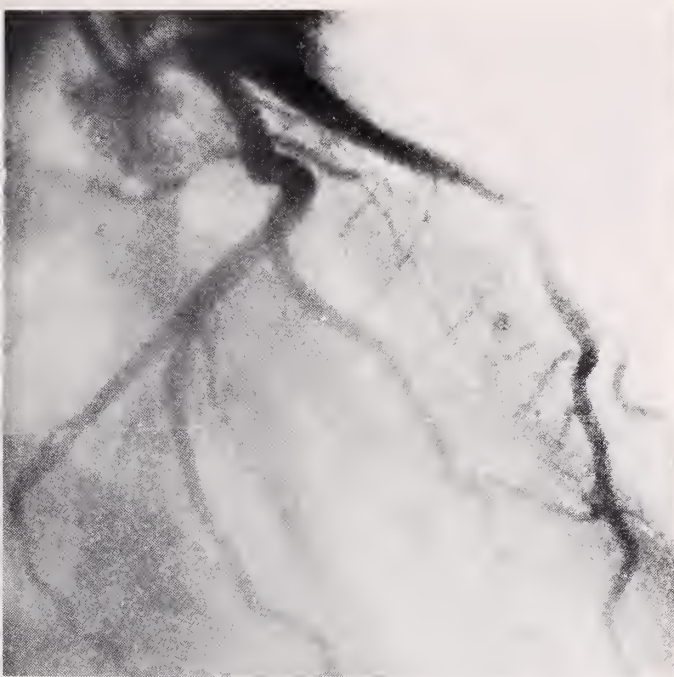


Fig. 1. Frames from a normal coronary cineangiogram showing the left coronary artery (left) and the right coronary artery (right) in the RAO position.

### RESULTS

Two hundred and fifty patients were studied by coronary arteriography. One hundred and ninety-one patients had significant coronary artery disease. Ninety-six patients were treated medically and 95 patients had coronary artery by-pass grafting. The mortality rate in both groups for this limited follow-up period was 10%. Fifty-nine patients had normal coronary arteriograms. Forty-four patients had coronary arteriography as part of the evaluation of valvular or other types of heart disease. Of the patients suspected of having ischemic heart disease, 88% had significant coronary artery disease and 12% had normal coronary arteries at the time of study. Fifty-six patients were considered to have unstable angina pectoris. Fifty-two of these had significant coronary artery disease and 4 had normal coronary arteries. Forty-six of 63 patients with chest pain of uncertain etiology had normal coronary arteriograms. Thirteen patients had more than 50% stenosis of the left main coronary artery and 12 of the 13 had associated severe two or three vessel disease.

Eighty-six patients surviving coronary artery by-pass grafting have been followed and, though the follow-up period is limited at the time of this writing, 65% are pain free, 26% are improved and 9% have not improved. Eight patients who had coronary artery by-pass surgery did not show improvement in their angina postoperatively. Most of these patients had severe two or three vessel disease with impaired left ventricular function characterized by increased heart size on chest x-ray raised left ventricular filling pressure and depressed ejection fraction. Seven of the 8 patients who failed to improve were restudied. Four of these had at least one

occluded graft, 2 of the 7 had narrowed grafts. In one patient, the coronary artery disease had progressed to involve a vessel which was not involved at the time of surgery.

Serious complications were infrequent (Table 1). One patient had delayed hemorrhage from the femoral artery puncture site and transfusion was required. No instance of femoral or brachial artery occlusion occurred. Pulmonary edema occurred on two occasions and responded to diuretics and nitrates. Chest pain requiring nitrates or narcotic for relief was frequent but no new infarctions occurred. One patient had ventricular tachycardia and one had ventricular fibrillation, both requiring direct counter shock. On both occasions the arrhythmia occurred during or shortly after the injection of a non-stenotic right coronary artery. One patient with extensive three vessel disease died of painless cardiac shock. No serious allergic reaction to the angiographic contrast material was noted. There was no instance of cerebral embolism or coronary artery occlusion/dissection.

The average "catheter in time" was 37 minutes in those studies where only coronary arteriography was performed and the average fluoroscopy time 12 minutes. Five studies were considered incomplete.

### DISCUSSION

The incidence of adverse reaction to coronary arteriography varies and is related to many factors which include the technique employed, the case load, the nature of the patient population, the duration of the procedure ("catheter in time"), the assistant personnel, the training and judgment of arte-

riographer and, possibly the use of heparin. The most important factors have been considered to be the technique employed and the case load of the institution.

The results of early studies suggested that the complication rate of coronary arteriography was greater with the transfemoral (Judkins) than with the brachial (Sones) technique. Based on questionnaires from 373 institutions with surgical teams (46,904 patients), the average mortality from coronary arteriography in 1972 was 0.45%, but was lower with the brachial approach (0.13 vs. 0.78%).<sup>1</sup> The excess risk with the transfemoral technique was considered to be related to thrombus formation on the guide wires and the lack of intensive training and experience among those performing the studies by the more easily learned transfemoral technique. However, the results of a similar survey of 89,079 patients studied at 179 institutions during 1973-74 revealed a striking reduction in the overall mortality with the transfemoral technique from 0.78 to 0.16% which did not differ significantly from 0.10% mortality associated with brachial approach.<sup>2</sup> This reduction in mortality was considered due to the accumulated experience of the operators. Others have reported a similar recent decrease in mortality, coincident with the use of heparin, but possibly related to other factors.<sup>8,11-15</sup> It appears, therefore, that the transfemoral technique (Judkins) is as safe as the brachial (Sones) approach.

One of the major determinants of the risk of coronary arteriography is thought to be the case load, or the number of examinations performed in a year. The previously cited studies reported that more complications were seen in institutions performing fewer than 100 examinations per year.<sup>1,2</sup> It seems equally pertinent, however, to relate the risk to the number of examinations performed by each cardiologist but this information is not usually available. One group of 7 cardiologists reported 3,089 studies during a five-year period with a mortality during the last twelve months of 0.53%.<sup>12</sup> Assuming that all cardiologists shared the load equally, an average of 90 examinations per cardiologist per year was performed. Another group of four cardiologists reported a 0.16% mortality in 627 patients over 33 months, an average of near 90 examinations per cardiologist per year.<sup>11</sup> During the first 29 months of operation, 437 catheterizations have been performed in our hospital including 250 selective coronary arteriograms or about 120 per year. Since all catheterizations are performed jointly by the same two cardiologists, the experience is maximized.

The most frequent complications of coronary arteriography include arterial thrombosis, serious ventricular arrhythmias, myocardial infarction, death, cerebral embolism, hemorrhage and pseudoaneurysm formation. The reported incidence of these complications varied widely but generally less than 1%.<sup>1-10</sup> Our complications are listed in Table 1.

TABLE 1

COMPLICATIONS OF CORONARY ARTERIOGRAPHY (250 Patients)		
Death .....	1	(0.4%)
Ventricular tachycardia/fibrillation .....	2	
Hemorrhage .....	1	
Pulmonary edema .....	2	
Incomplete study .....	5	

TABLE 2

MORTALITY FROM CORONARY ARTERIOGRAPHY (TRANSFEMORAL TECHNIQUE)		
	Number of Patients	Percent Mortality
Adams <sup>1</sup> (1973)	22,780	0.78
Green <sup>5</sup> (1972)	455	0.45
De la Torre <sup>6</sup> (1973)	139	1.4
Abrams <sup>2</sup> (1975)	89,079	0.16
Bourassa <sup>9</sup> (1976)	5,250	0.23
Wolfson <sup>10</sup> (1976)	800	0.87
Weaver <sup>11</sup> (1976)	593	0.50
Page <sup>12</sup> (1975)	3,089	0.35

The one death in our series was not thought to be related to a thrombo-embolic complication. Post-mortem study of this patient confirmed the extensive three vessel disease shown on coronary arteriography. There was no evidence of infarction by the usual gross and microscopic techniques and no recent arterial occlusion was found. We suspect that this death may have been related to an unusual reaction to the contrast material as described by Caulfield.<sup>16</sup> Their patients, like ours, developed progressive painless dyspnea and shock during or shortly after coronary arteriography. Post-mortem examination of their six patients did not show new coronary arterial occlusion or infarction but did show extensive coronary arterial disease and easily visible contrast material within the intramyocardial venous system. It has been proposed that the contrast material, washed out slowly because of the decreased coronary arterial blood flow, chelated the myocardial calcium and irreversibly depressed myocardial function.

Most patients requiring coronary arteriography have serious ischemic heart disease and are in a high risk stage of the natural history of their disease. Indeed, Hilder observed that a large number of deaths occurred in the 48 hours before and 24 hours after a scheduled catheterization even when the procedure was not performed.<sup>17</sup> The risk of coronary arteriography is a function of the patient population studied and seems to be related to the severity of the coronary artery disease.<sup>7,10,18,19</sup> Thus, the mortality of any given institution is related to the number of "high risk" patients studied. Most studies dealing with mortality of coronary arteriography have not indicated the character of the patient population. The so-called "high risk group" is composed of patients with left main coronary artery disease and the triple vessel coronary artery disease which is almost invariably present. The risk of studying these patients has been considered high (6-15%),<sup>2,7,18,19</sup> al-

though not all groups have not had this experience.<sup>20-21</sup> Thirteen of our patients (5.2%) had at least 50% stenosis of the left main coronary artery and 12/13 patients had associated two or three vessel disease. Our experience does not include the death of a patient with left main coronary disease but, based on the experience of others, we have taken unusual care of patients with patients suspected of having left main disease as suggested clinically by unstable angina, pain associated with dyspnea and marked ST segment depression (greater than 2 mm.) on exercise EKG. In these patients, cusp injections of the left coronary ostium are routinely performed in a shallow RAO position and, if left main disease is found, the number of injections is curtailed to the absolute minimum.

Many factors other than the case load, the patient population, and the technique employed affect mortality of coronary arteriography. As Weaver emphasized, the incidence of complications seems to be related to the duration of the procedure, or "catheter in time."<sup>11</sup> Other studies support this view.<sup>22,23</sup> The duration of the procedure is doubtless related to the experience and expertise of the operator, but other delays may be caused by associated physiologic studies performed in institutions engaged in training programs and clinical research. We have made an effort to keep "catheter in time" to a minimum avoiding the acquisition of less critical data. The average catheter-in-time for coronary arteriography in our laboratory is 37 minutes and the average fluoroscopy time 12 minutes.

Many of the complications of coronary arteriography have been thrombo-embolic. Thrombus formation on the catheter and guide wires is related not only to the time within the vascular system but also to the catheter material used. The internal surface of polyurethane catheters is very irregular and these surface irregularities seem to play a major role in thrombus formation.<sup>24</sup> Polyethylene catheters on the other hand are more smooth and regular and appear to be less thrombogenic.<sup>25</sup> Clot formation seems to occur much more rapidly on the teflon coated guide wires than on stainless steel ones so that the combination of teflon coated guide wires and polyurethane catheters is at least theoretically an undesirable one.<sup>26</sup> We have used polyethylene catheters (Cook) and teflon coated guide wires and have had no thrombo-embolic complications. We have routinely used systemic heparinization. Whether or not systemic heparinization has been generally beneficial is controversial but many groups have reported a decrease in complications coincident with routine use of heparin.<sup>8,11-15</sup> Since the use of heparin seems to decrease the incidence of thrombo-embolic complication and has not been associated with unfavorable results its use seems, for the present time, prudent.

Michie observed elevation of creatine phosphokinase (CPK) activity following coronary arteriography and proposed that intracoronary injection of

contrast material was responsible for this rise.<sup>27</sup> If this were so, the interpretation of elevated serum CPK activity after coronary arteriography would be difficult and could not be used as a reliable indicator of myocardial infarction occurring during or following coronary arteriography. It has been shown subsequently, however, that the rise in CPK activity following uneventful coronary arteriography is probably related to the intramuscular injection of premedication rather than the intracoronary contrast and that CPK activity could be useful in excluding myocardial infarction if oral premedication were used.<sup>28</sup> Our experience agrees with Metlof and suggests that serum CPK activity does not increase as the result of the intracoronary injection of contrast material per se. In 125 of our patients, values for CPK after coronary arteriography were available for review. Although chest pain occurred during the procedure on a number of occasions, in no instance were there significant EKG changes and serum CPK activity did not rise unless intramuscular injections had been given. MB-CPK, the cardiac fraction of creatine phosphokinase, does not rise following intramuscular injections even though the total CPK activity may be elevated, and this determination may be useful in excluding myocardial necrosis.<sup>29</sup> However, this determination is not universally available, is somewhat more expensive and the use of oral premedication has been very satisfactory in our experience and its use preserves the usefulness of the CPK determination in the differential diagnosis of chest pain occurring during or after coronary arteriography.

Although this study was not designed to be a follow-up evaluation of coronary artery by-pass surgery, the preliminary results are interesting. The majority (88%) of patients operated were either pain free or symptomatically improved in the follow-up period (6 to 24 months). In all but 1 of the 9% of patients who were not improved following surgery, there was residual ischemic myocardium — that is, either an occluded or narrowed graft or progression of the coronary artery disease to involve vessels not involved at the time of surgery. It appears, therefore, that if the ischemic myocardial segment is satisfactorily revascularized symptomatic improvement is the result.

#### SUMMARY

Coronary arteriography is very useful in the management of patients with, and those suspected of having, coronary artery disease. Our experience suggests that with attention to detail, this very useful but potentially dangerous procedure can be performed at low risk in a non-university affiliated regional hospital. The primary objective of these studies should be the satisfactory opacification of the coronary arterial system and evaluation of the functional state of the left ventricle keeping catheter-in-time to a minimum.

# ACKNOWLEDGEMENTS

We are grateful to the members of the Radiology staff, and to Helen McLain, Carrol Gallupe, Kathy Tamm, Peggy Wentworth and Deborah Campbell who provided valuable technical assistance.

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# Rational Use of Antibiotics

Colby Weekend College — Postgraduate Medical Education  
Sponsored With the Maine Medical Association and the Mid-Maine Medical Center  
March 5 and 6, 1977, Colby College, Waterville, Maine

# Saturday, March 5

- 10:00-10:30 A.M.  
Diagnosis of Infection — Role of Gram Stain and Culture  
Robert Wise, M.D., Togus, Maine
- 10:30-11:00 A.M.  
Effective New Antibiotics  
Thomas Claffey, M.D., Portland, Maine
- 11:00-12:00 M.  
Workshop
- 12:00 M.-1:00 P.M.  
Lunch
- 1:00-1:30 P.M.  
Upper Respiratory Tract Infections  
David R. Ginder, M.D., Waterville, Maine
- 1:30-2:00 P.M.  
Community Acquired Pneumonias  
GUEST SPEAKER: Arnold Weinberg, M.D., Professor of Medicine, Harvard
- 2:00-3:00 P.M.  
Workshop
- 3:00-3:30 P.M.  
Recess
- 3:30-4:00 P.M.  
Infectious Diarrhea  
William Hall, M.D., Portland, Maine
- 4:00- 4:30 P.M.

- Hepatitis  
William Nersesian, M.D., Augusta, Maine
- 4:30-5:30 P.M.  
Workshop
- 6:00-7:00 P.M.  
Cocktails
- 7:00-8:00 P.M.  
Dinner
- 8:00-9:00 P.M.  
Gynecologic Infections  
GUEST SPEAKER: Arnold Weinberg, M.D., Professor of Medicine, Harvard

# Sunday, March 6

- 9:00-9:30 A.M.  
Urinary Tract Infection  
Bruce Denny-Brown, M.D., Bangor, Maine
- 9:30-10:00 A.M.  
Gonorrhea  
Peter Leadley, M.D., Waterville, Maine
- 10:00-11:00 A.M.  
Workshop
- 11:00-12:00 M.  
Nosocomial Infection  
Michael Bach, M.D., Lewiston, Maine
- 12:00 M.-1:00 P.M.  
Workshop

Fee: \$85.00 (Includes course fee and Saturday lunch, reception and banquet). Minimum Enrollment: 30; Maximum Enrollment: 60.  
For further information write to: Robert Kany, Colby College, Waterville, Maine 04901.

# Alternate Exposure, Biplane, Magnification Angiography: A Modern Neuroangiographic System

JOHN M. LONG, M.D.\*

During the Fall of 1975, a new method of performing cerebral angiography was initiated in the Department of Radiology at the Eastern Maine Medical Center. The past year's experience with this new technology has proven quite satisfactory, yielding excellent resolution and high contrast arteriograms with reduced hazard to the patient.

The use of direct serial magnification should not be considered only the tool of clinical investigation. Most radiology departments with modern neuro-radiology sections are employing magnification techniques frequently, if not routinely, for their neuroangiographic procedures. By increasing the image size and improving the image resolution, the magnification technique reduces the incidence of false-positive errors.<sup>1</sup>

As in the majority of institutions where cerebral angiography is frequently performed, the case load of cerebral angiography at Eastern Maine Medical Center is insufficient to tailor the special procedure suite specifically for the needs of the neuroangiographic procedures alone. The room must be designed in such a manner as to be compatible with the general angiographic and cardiac procedures. A system of monoplane, magnification cerebral angiography designed for the community hospital where all types of special procedures including myelograms and bronchograms must be performed in the same room, has been previously described.<sup>2</sup> The system to be discussed below is appropriate for the special procedure suite dedicated to angiographic procedures and where a significant number of neuroangiographic studies are performed. At EMMC, we average nearly two neuroangiographic studies per day.

## METHOD

Biplane, magnification arteriography has the advantage of requiring a single injection to film both frontal and lateral views. The major objection to biplane work has been that the scattered radiation from each tube causes an increase in baseline density in the opposite plane which reduces film contrast, resulting in a generally inferior image. A system of simultaneous exposure, biplane magnification arteriography utilizing both air gap and grids to eliminate scattered radiation, has been developed at the University of Minnesota.<sup>3</sup> The disadvantage of this system is the relatively high exposure necessary because of the grid system which,

in addition to absorption of scattered radiation, absorbs a certain percentage of primary radiation. Their system is the only one possible without unacceptable film waste, when roll film changers are used. With the cut film type of changer, the magazines can be alternately loaded so that odd chambers are filled for the frontal projection and even positions for the lateral plane. When the film in one plane is being exposed there is an empty slot in the opposite film changer, hence, the air gap suffices to clear up the scattered radiation and a grid and resulting increased exposure is not necessary.

At EMMC, our standard magnification factor is approximately 1.7X. This is attained by positioning the film changer 36 inches from the focal spot of the x-ray tube. A 15 inch air gap is employed. In the lateral plane, this distance is measured between the center of the side of the head being examined and the film. Since the lateral film changer is always on the patient's left side, this will allow for roughly the same degree of magnification no matter which side is injected. The 1.7X factor was selected after a trial with both 2X and 1.5X factors. The resolution was found to be the best at 1.7X with our nominal 0.3 mm focal spot. A 36 inch focal film distance was selected rather than the standard 40 inch in order to take advantage of the inverse square law and resultant increase in effective milliamperage seconds (MAS).

Microfocus x-ray tubes are essential components of any magnification film system.<sup>4</sup> Without the fractional focal spot tube, moving the object away from the recording plane will result in image enlargement concomitant with enlargement of its edge unsharpness. This is the same effect as optical, not geometrical magnification. There is increase in the size of the image but no increase in its resolution. We employ Siemens Biangulex 150/12/101R nominal 0.3 mm focal spot size tubes in each plane. Current standards allow up to plus 50% variation in actual measurement of focal spots leading some authors to suggest that a 0.2 mm focal spot is more ideal for standard neuroangiographic studies.<sup>5</sup> Current restrictions on these fractional focal spot tubes are quite stringent. Our system allows only 10 MAS, a 0.08 second exposure at 125 MA. Further increase in the MA results in unacceptable "ballooning" of the focal spot, a result of excessive anode heating. This causes poor resolution and short tube life. By maintaining kilovoltage (KV) in the 70's and 80's at 10 MAS, we do not exceed tube heating restrictions for a series of eleven films.

AOT Elema-Schonander film changers have

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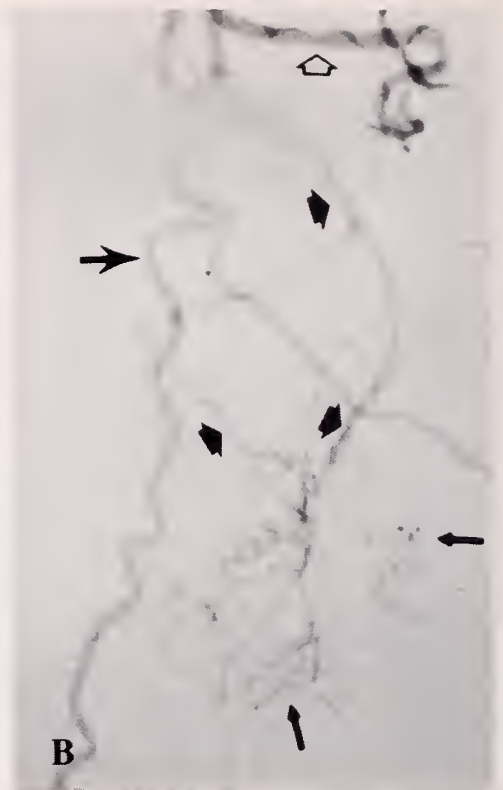
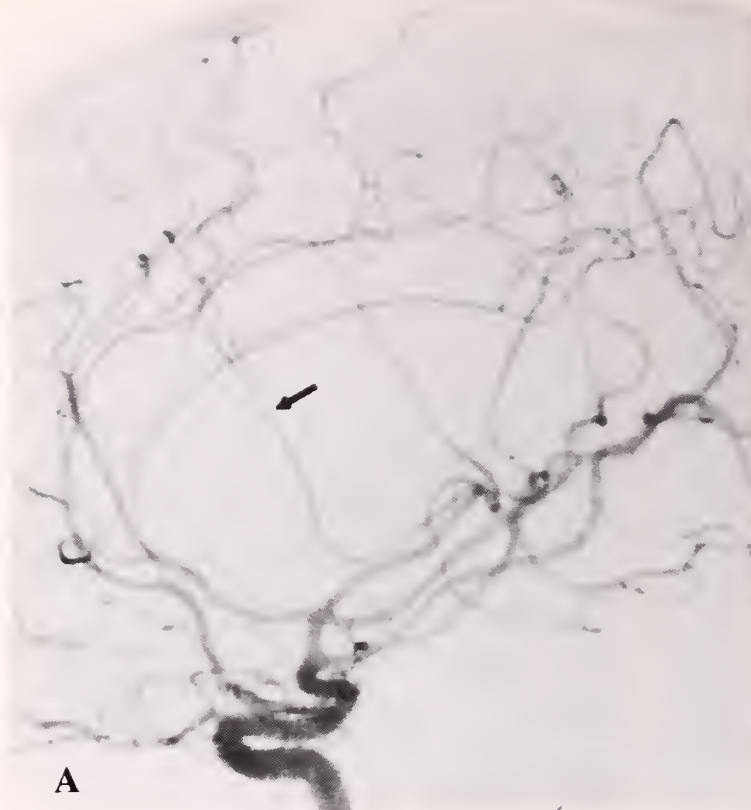


Fig. 1. Meningioma.

A. Lateral View Internal Carotid Arteriogram. There is marked stretching of the ascending frontal branches (arrows) of the middle cerebral artery and inferior displacement of the anterior portion of the sylvian triangle. No tumor stain is present.

B. Lateral View External Carotid Arteriogram. The middle meningeal artery is greatly enlarged (arrowheads) and tumor vascularity is apparent (arrows). NOTE normal maxillary artery (open arrowhead) and superficial temporal artery (large arrow).

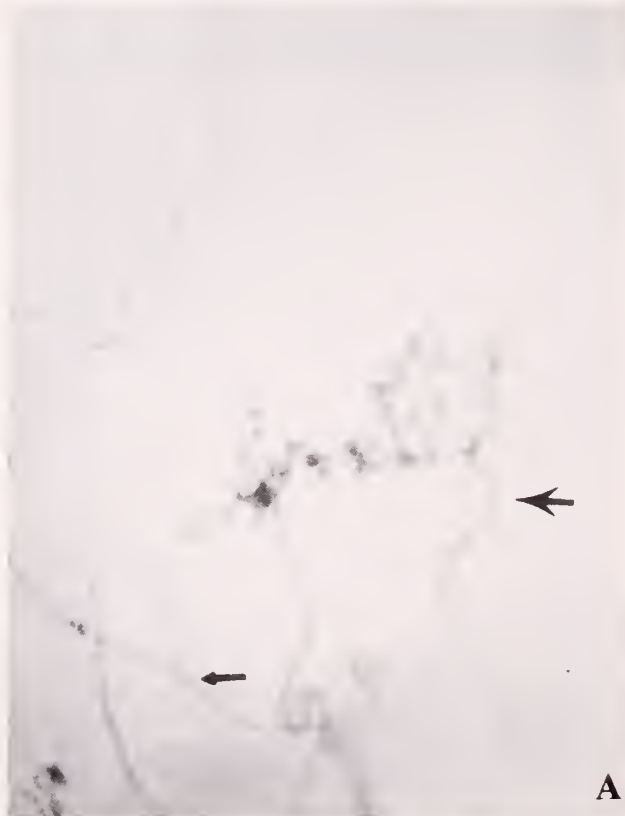


Fig. 2. Scalp Hemangioma — Left External Carotid Arteriogram.

A. A vascular tumor is demonstrated. The superficial temporal artery is enlarged and supplies the tumor (large arrow). The middle meningeal artery is normal (arrowheads).

B. Anterior posterior view demonstrating the tumor in an extracranial location. The internal carotid arteriogram demonstrated no intracranial abnormality.

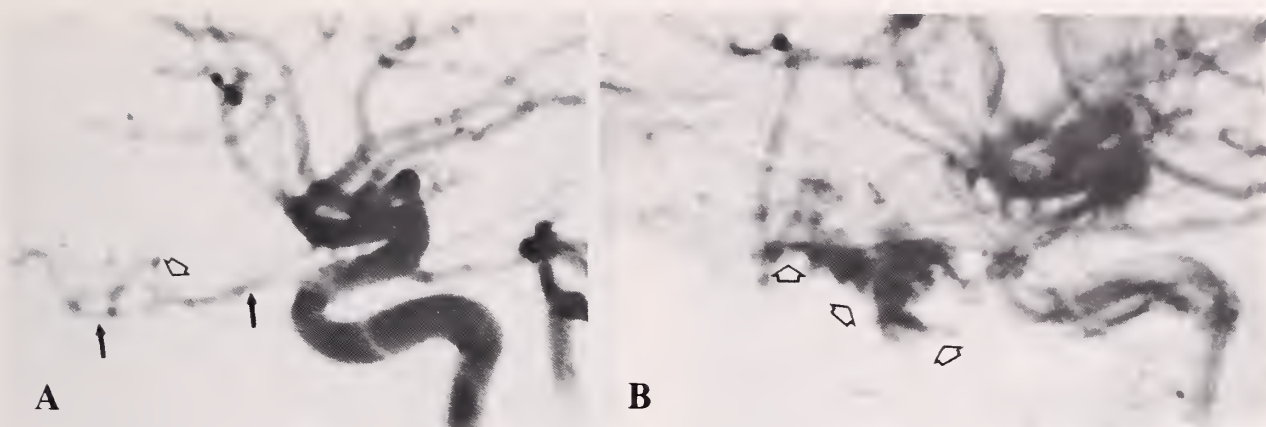


Fig. 3. Orbital Angioblastic Meningioma with Intracranial Extension.

A. Lateral view internal carotid arteriogram. The ophthalmic artery is enlarged (arrows). Early tumor stain can be seen (open arrowhead).

B. Late arterial phase. A dense homogeneous tumor stain extending through the superior orbital fissure and into the middle cranial fossa is now apparent (open arrowheads).

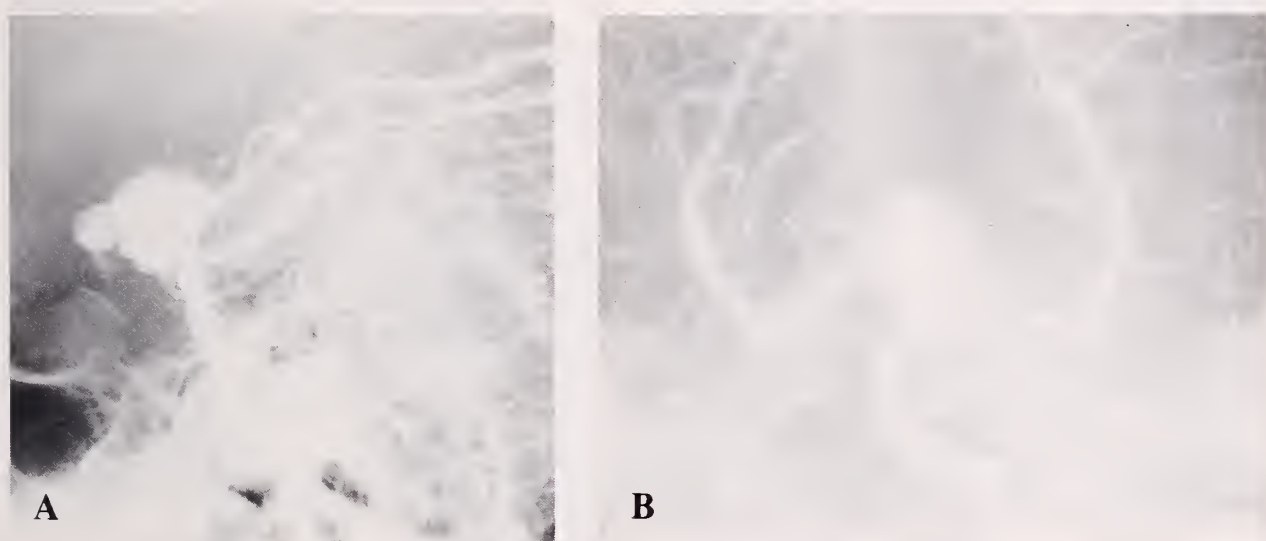


Fig. 4. Basilar Tip Aneurysm.

A. Lateral vertebral arteriogram. A large bilobed aneurysm is demonstrated arising from the tip of the basilar artery.

B. Towne view.

proven optimal for this system. The magazines can be "skip loaded" using even slots for one plane and odd slots for the opposite. A total of fifteen films may be loaded in this fashion. In order to obtain two exposures per second, the alternately loaded film changer is run at four frames per second. An x-ray exposure is not triggered unless a film is in position between the film screens, hence, only two films are exposed in each plane per second. When an exposure is being made in our plane, no film is in place in the alternate plane to be fogged. After the first two seconds, the film changer program is altered to two frames per second giving one film per second in each plane for the duration of the series which is generally seven additional films. The limiting factor here is the film transit time. In order to utilize the film changer at four frames per second, the maximum exposure time allowed is 80 milliseconds.

This system demands a fast film intensifying screen combination.

Kodak rare earth screens (Lanex) and Ortho G film has been selected for this system for several reasons. Primarily, the combination is extremely fast and allows adequately exposed magnification films with an average of 65 and 85 KV at 10 MAS respectively in the lateral and frontal planes. The KV range is satisfactory to maximize the contrast properties of the iodine containing contrast agent. The other major advantage of rare earth intensifying screens is in decreased radiation dose which is no minor consideration when nearly seventy radiographic exposures are made in a complete cranial investigation. It is emphasized that there is no increase in exposure in progressing from no magnification to a 2X magnification study.<sup>6</sup> There is no significant degradation of the image in my judgment



Fig. 5. Ulcerated and Stenotic Atherosclerotic Disease.  
A. Lateral cervical carotid arteriogram. A highly stenotic and ulcerated atherosclerotic lesion is demonstrated in the right internal carotid artery (arrow). Many other plaques are present.  
B. Anterior-posterior view. The severely stenotic internal carotid artery is superimposed on the external carotid vessel (arrowhead).

and the life of the screens has been at least as long as standard intensifying screens.

In order to vary the magnification factor and keep the same factor in each plane, an x-ray table with a vertical rise capability is required. The increased object film distance in the frontal plane is then easily obtained by raising the table and patient above the frontal film changer. Raising the rather massive AOT film changer in the lateral plane to be at the level of the patient's head is a bit more difficult. We have mounted the film changer on the pedestal of an old dental chair. The AOT is pumped up to the proper level and moved away the appropriate distance from the patient's head.

In general, the 15 inch air gap is sufficient to clean up the secondary radiation but the film image quality is further improved by the use of lead cut outs. We employ a series of these with different diameters and keyholes which are interchanged depending on the patient's head size and the portion of the anatomy to be demonstrated. In addition, tight collimation is employed. We attempt to allow no margin of exposure around the skull.

Our pressure injector is wired in with the film programmer so that an appropriate delay of injection or film changer may be selected in order to obtain one blank film for a subtraction mask. The radiologist is then out of the room during the exposure and observes the injection through a leaded glass window. One exception is during vertebral angiography. Despite the use of 5-French catheters in adults and 4-French in children, the catheter is immediately withdrawn after the injection, not the entire film sequence, to avoid spasm. In this



Fig. 6. Angiographic Suite.  
The table is in position for a biplane, magnification cerebral arteriogram. Note the distance between the microfocus x-ray tubes (arrows), the pad for the patient's head (white arrowhead), and the film changers (large arrows).

situation, the radiologist stands behind a portable lead barrier which has been wheeled into position.

Two 1200 MA, three phased Gigantos Siemens x-ray generators are used to power the x-ray tubes. These large generators are not specifically required for the relatively low MA needed for cerebral magnification studies but are helpful in obtaining rapid peak kilovoltage without significant "ripple." Higher MA requirements are necessary for abdominal and thoracic procedures which are performed in the same suite.

#### COMMENT

I have observed that many Departments of Radiology could easily perform magnification angiography with a few relatively minor adjustments including the addition of a microfocus x-ray tube. A return in increased film quality fully justifies the expense. For the department performing only occasional cerebral angiograms, a monoplane system may be more practical and is certainly less ex-

pensive.<sup>2</sup> In our Center, the biplane system is ideal. Ironically, it is not the newly demonstrated, subtle information that seems to account for the improved accuracy with this technique, rather the clear and concise depiction of information present, but more easily overlooked on standard cerebral angiograms.

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# The Richards Drug Classification

A. DEWEY RICHARDS, M.D.\*

In the development of a family practice residency program, one of the major considerations is the establishment of rational and reliable methods of auditing the performance of the residents. The American Academy of Family Physicians and others have strongly recommended documentation of the diagnoses treated and the procedures done by family practice residents in their training. The problems commonly dealt with in ambulatory care are often chronic and frequently require long-term drug therapy, occasionally with multiple agents. The three areas where audit of performance and documentation of activity seems most important are 1) the diagnoses dealt with, 2) the procedures done, and 3) the medications prescribed.

The WONCA International Classification of Health Problems in Primary Care is an international classification of diagnoses assembled on a logical basis and widely published.<sup>1</sup> The four-digit code is easy to use by the residents, the office staff, and the computer programmers. A similar organization of procedures is the Current Procedural Terminology (CPT).<sup>2</sup> It is also widely distributed and accepted. This utilizes a five-digit code which is somewhat cumbersome for some computers. The State of Maine Medicare fiscal intermediary modified this to four digits to make it more easily handled by their computer. The State of Maine Medicaid computer is also programmed for the four-digit modification of the ICD. In my attempt to get the hospital computer programmed to handle the ICD, I was again told that the five-digit code was too cumbersome for the hospital's computer so the four-digit code will be used there also.

A literature search for a suitable drug code revealed two probably related facts. First, there was no drug classification utilizing five digits or less in a systematic code. Second, very few family practice residency programs record drug usage in the same manner that they record diagnoses and procedures. The few programs which have established the capability of recording and examining all prescriptions find this very useful, although quite expensive.<sup>3</sup>

T. Donald Rucker, Ph.D., has proposed a computerized drug information system which would upgrade the quality and rationality of health care and provide a means for ongoing peer review of medications prescribed.<sup>4</sup> Dr. Rucker's estimated price tag of \$600 million for a computer network connecting all physicians and faculties to a government bureau makes implementation of his plan un-

likely; however, his plea for more comprehensive, more accessible data on actual prescribing practices was felt to be "a point well taken" by his most vocal critic.<sup>5</sup> It is our hope that the development of the Richards Drug Classification will make it possible to develop useful data without the massive expenditure of money suggested by Dr. Rucker.

The literature describing the need for a drug code is clear. Joan Ritchie in the *Lancet* of March 8, 1975, described a system for drug identification utilizing a complex system of cards, colors, and characteristics. She noted that "the Committee on Identification of Drugs had decided that a scheme of identification by letters and numbers would be impractical but not impossible."<sup>6</sup> The new classification will make it possible to mark each tablet with these digits, so that the drug in question can be easily identified.

Dr. Frank Ascione has described the difficulty in separating fact from fiction in evaluating drug interactions. He noted that the in vitro observations, isolated clinical observations, and animal studies do not give the reliable data available from human studies. Traditionally, human studies on drug interactions have been either anecdotal, epidemiologic, or controlled trials. The lack of reliable data collected prospectively on simultaneous usage of medications has hampered discovery and verification of possible drug interactions.<sup>7</sup>

The need for a simple, logical classification of drugs used in ambulatory care was very apparent. With no such classification and code available, it was decided that a classification code would be developed for the purposes of the Eastern Maine Medical Center's Family Practice Residency Program.

It was determined that the code should be rational with the first digit indicating a general group of drugs, the second digit a major subdivision, and the third digit a generic equivalent grouping wherever feasible. It was also stipulated that the code should include all the drugs used in ambulatory care. It was felt that the code should be as short as possible, containing as few categories as are consistent with the above qualifications. The resulting classification code meets the above criteria and is now in use at the Eastern Maine Medical Center's Family Practice Residency Program.

Each patient seen has a Patient Contact Record (Figure 1) filled out. The procedure done is indicated, the diagnoses dealt with are indicated, and the drugs the patient is currently using are noted. The data, plus the patient's demographic data, the physician and paraprofessionals treating the pa-

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*Text is Continued on Page 24*



## RICHARDS DRUG CLASSIFICATION

July 1976 Working Version of Three-Digit Numerical Code Designed to Include All Drugs Used in Ambulatory Care

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### I Antihistamines, Expectorants, Antitussives, Anorexiant, Antineoplastics

#### 1 Antihistamines

- 111 Brompheniramine
- 112 Pheniramine and Chlorpheniramine
- 113 Dexbrompheniramine
- 114 Dexchlorpheniramine
- 115 Chlorcyclizine
- 116 Cyclizine
- 117 Meclizine
- 118 Cyproheptadine HCl
- 119 Dimethindene

#### 2 Antihistamines

- 121 Dimenhydrinate
- 122 Diphenhydramine
- 123 Diphenylpyraline HCl
- 124 Promethazine HCl
- 125 Trimeprazine
- 126 Tripeleminamine
- 127 Triprolidine
- 128 Pyrillamine
- 129 Methapyrilene
- 120 Other Antihistamines

#### 3 Expectorants

- 131 Acetylcysteine
- 132 Ammonium Chloride
- 133 Calcium Iodide
- 134 Glyceryl Guaiacolate
- 135 Potassium Iodide
- 136 Terpin Hydrate
- 137 Wild Cherry Syrup
- 130 Other Expectorants

#### 4 Antitussives

- 141 Pipazethate
- 142 Benzonatate
- 143 Carbetapentane
- 140 Other Antitussives

#### 5 Anorexiants

- 151 Diethylpropion HCl
- 152 Phenmetrazine HCl
- 153 Phendimetrazine HCl
- 154 Phentermine
- 155 Chlorphentermine
- 156 Mazindol
- 157 Chlortermine HCl
- 158 Fenfluramine HCl
- 150 Other Anorexiants

#### 6 Antineoplastics

- 161 Busulfan
- 162 Chlorambucil
- 163 Cyclophosphamide
- 164 Mechlorethamine
- 165 Melphalan
- 166 Triethylenethio-phosphoramide
- 167 Cytarabine

- 168 Fluorouracil
- 169 Mercaptopurine

#### 7 Antineoplastics

- 171 Methotrexate
- 172 Thioguanine
- 173 Blenmycin
- 174 Dactinomycin
- 175 Doxorubicin
- 176 Mithramycin
- 177 Mitomycin
- 178 Daunorubicin
- 179 Dacarbazine

#### 8 Antineoplastics

- 181 Hydroxyurea
- 182 Procarbazine
- 183 Vinblastine
- 184 Vincristine
- 185 BCNU\*
- 186 Methyl CCNU\*
- 187 Calcium Leucovorin
- 188 Daunomycin
- 189 Galactitol
- 180 Other Antineoplastics

\* — Investigational

## II Antiinfectives

#### 1 Amebicides, Anthelmintics

- 211 Carbarsone
- 212 Diiodohydroxyquin
- 213 Emetine
- 214 Metronidazole
- 215 Mebendazole
- 216 Piperazine
- 217 Pyvinium Pamoate
- 210 Other Amebicides and Anthelmintics

#### 2 Antifungals

- 221 Amphotericin B
- 222 Flucytosine
- 223 Griseofulvin
- 224 Iodochlorhydroxyquin
- 225 Nystatin
- 226 Tolnaftate
- 227 Gramacidin
- 220 Other Antifungals

#### 3 Penicillins

- 231 Penicillin G
- 232 Phenoxymethyl Penicillin V
- 233 Amoxicillin
- 234 Cloxacillin and Dicloxacillin
- 235 Oxacillin
- 236 Ampicillin

- 237 Carbenicillin
- 238 Methicillin
- 239 Nafcillin
- 230 Other Penicillins

#### 4 Erythromycins, Tetracyclines

- 241 Erythromycin
- 242 Tetracycline, Oxy and Chlor
- 243 Demeclocycline HCl
- 244 Doxycycline
- 245 Minocycline
- 240 Other Erythromycins, Tetracyclines

#### 5 General Antibiotics

- 251 Bacitracin
- 252 Cefalosporins
- 253 Chloramphenicol
- 254 Clindamycin
- 255 Colistimethate, Na, and Colistin Sulfate
- 256 Trimethoprim
- 257 Nalidixic Acid
- 258 Nitrofurantoin
- 259 Methenamine Mandelate

#### 6 General Antibiotics

- 261 Gentamicin Sulfate
- 262 Kanamycin Sulfate
- 263 Neomycin Sulfate
- 264 Novobiocin
- 265 Polymixin B Sulfate
- 266 Spectinomycin
- 267 Streptomycin Sulfate
- 268 Vancomycin
- 269 Tobramycin
- 260 Other General Antibiotics

#### 7 Sulfa Drugs and Urinary Antiseptics

- 271 Acetosulfone Sodium
- 272 Phenazopyridine
- 273 Salicylazosulfapyridine
- 274 Sulfacetamide
- 275 Sulfisoxazole
- 276 Sulfamethizole
- 277 Sulfamethoxazole
- 278 Sulfathiazole
- 279 Trisulfapyrimidines
- 270 Other Sulfa Drugs

#### 8 Antituberculars

- 281 Aminosalicilate Na
- 282 Cycloserine
- 283 Ethambutol HCl
- 284 Ethionamide
- 285 Isoniazid
- 286 Pyrazinamide
- 287 Rifampin
- 288 Viomycin
- 280 Other Antituberculars

- 9 *Plasmodicides* (Antimalarials)
  - 291 Chloroquine Phosphate
  - 292 Hydroxychloroquine
  - 293 Pyrimethamine
  - 294 Quinine Dihydrochloride
  - 295 Quinine Sulfate
  - 296 Amodiaquine HCl
  - 290 Other Plasmodicides

### III Autonomic

- 1 *Parasympathomimetic*
  - 311 Acetylcholine Chloride
  - 312 Bethanechol Chloride
  - 313 Carbachol
  - 314 Demecarium Bromide
  - 315 Echothiophate Iodide
  - 316 Edrophonium Chloride
  - 317 Neostigmine Bromide
  - 318 Physostigmin Salicylate
  - 319 Pilocarpine
  - 310 Other Parasympathomimetic
- 2 *Parasympatholytic*  
(Cholinergic Blocker)
  - 321 Atropine Sulfate
  - 322 Homatropine Methyl Bromide
  - 323 Belladonna
  - 324 Benztropine Mesylate
  - 325 Mepenzolate
  - 326 Dicyclomine HCl
  - 327 Cyclopentolate HCl
  - 328 Isopropamide
  - 329 Methantheline Bromide
- 3 *Parasympatholytic*  
(Cholinergic Blocker)
  - 331 Scopolamine HBr
  - 332 Methscopolamine Br
  - 333 Propantheline Bromide
  - 334 Trihexyphenidyl
  - 330 Other Parasympatholytic
- 4 *Sympathomimetic*
  - 341 Dopamine HCl
  - 342 Ephedrine Sulfate
  - 343 Epinephrine
  - 344 Isoproterenol
  - 345 Metaraminol Bitartrate
  - 346 Phenylpropanolamine
  - 347 Phenylephrine
  - 348 Pseudoephedrine
  - 349 Terbutaline Sulfate
  - 340 Other Sympathomimetic
- 5 *Sympatholytic*
  - 351 Ergotamine Tartrate
  - 352 Methysergide Maleate
  - 353 Phentolamine
  - 354 Tolazoline
  - 350 Other Sympatholytic
- 6 *Skeletal Muscle Relaxants*
  - 361 Carisoprodol
  - 362 Chlorphenesin Carbamate
  - 363 Chlorzoxazone
  - 364 Gallamine Triethiodide
  - 365 Methocarbamol
  - 366 Succinylcholine Chloride
  - 367 Tubocurarine Chloride
  - 368 Orphenadrine
  - 369 Dantrolene Sodium
  - 360 Other Skeletal Muscle Relaxants

### IV Central Nervous System

- 1 *Antidepressants*
  - 411 Amitriptyline
  - 412 Desipramine
  - 413 Doxopin
  - 414 Imipramine
  - 415 Nortriptyline
  - 416 Protriptyline
  - 417 Isocarboxazid
  - 418 Phenelzine
  - 419 Tranlycypromine
  - 410 Other Antidepressants
- 2 *Major Tranquilizers*
  - 421 Acetophenazine
  - 422 Chlorpromazine
  - 423 Fluphenazine
  - 424 Perphenazine
  - 425 Prochloroperazine
  - 426 Promazine
  - 427 Thioridazine
  - 428 Trifluoperazine
  - 429 Triflupromazine
  - 420 Other Phenothiazines
- 3 *Major Tranquilizers*
  - 431 Butaperazine
  - 432 Chlorazepate Dipotassium
  - 433 Thiothixene
  - 434 Droperidol
  - 435 Chlorprothixene
  - 436 Haloperidol
  - 437 Lithium Carbonate
  - 438 Mesoridazine Besylate
  - 439 Piperacetazine
  - 430 Other Major Tranquilizers
- 4 *Minor Tranquilizers*
  - 441 Hydroxyzine
  - 442 Chlordiazepoxide
  - 443 Diazepam
  - 444 Flurazepam
  - 445 Oxazepam
  - 446 Ethchlorvynol
  - 447 Glutethimide
  - 448 Meprobamate
  - 440 Other Minor Tranquilizers
- 5 *Sedatives*
  - 451 Methaqualone
  - 452 Methypylon
  - 453 Paraldehyde
  - 454 Phenobarbital
  - 455 Pentobarbital
  - 456 Butobarbital
  - 457 Secobarbital
  - 458 Chloral Hydrate
  - 459 Other Non-Barbiturate Sedatives
  - 450 Other Barbiturates  
Amobarbital  
Hexobarbital  
Mephobarbital  
Methohexital  
Thiopental Sodium
- 6 *Respiratory and Cerebral Stimulants*
  - 461 Ammonia
  - 462 Caffeine
  - 463 Dextroamphetamine Sulfate and Methamphetamine
  - 464 Doxapram
  - 465 Ethamivan

- 466 Benzphetamine HCl
- 467 Methylphenidate
- 468 Nikethamide
- 469 Pentyleneetetrazol
- 460 Other Respiratory and Cerebral Stimulants

### 7 Anticonvulsants

- 471 Carbamazepine
- 472 Clonazepam
- 473 Ethosuximide
- 474 Diphenylhydantoin and Allantoin
- 475 Mephentoin
- 476 Phenacemide
- 477 Primidone
- 478 Paramethadione
- 479 Trimethadione
- 470 Other Anticonvulsants

### 8 Analgesics, Antipyretics, and Antiinflammatory

- 481 Acetaminophen
- 482 Salicylates
- 483 Ibuprofen
- 484 Indomethacin
- 485 Pentazocine
- 486 Phenacetin
- 487 Phenylbutazones
- 488 Propoxyphen
- 489 Dipyron and Antipyrone
- 480 Other Analgesics, Antipyretics, and Antiinflammatory

### 9 Analgesics (Narcotic)

- 491 Codeine
- 492 Meperidine
- 493 Methadone
- 494 Morphine
- 495 Dihydrocodienone
- 496 Hydromorphone
- 497 Paregoric
- 498 Dextromethorphan
- 490 Other Analgesics (Narcotic)

### V Cardiac-Blood

#### 1 Cardiac Drugs

- 511 Digitoxin
- 512 Digoxin
- 513 Deslanoside
- 514 Ouabain
- 515 Digitalis Leaf
- 516 Procainamide HCl
- 517 Propranolol HCl
- 518 Quinidine Sulfate
- 519 Sodium Nitroprusside
- 510 Other Cardiac Drugs

#### 2 Antilipemic, Arteriosclerosis

- 521 Clofibrate
- 520 Other Antilipemic, Arteriosclerosis

#### 3 Hypotensive Agents

- 531 Clonidine
- 532 Diazoxide
- 533 Guanethidine Sulfate
- 534 Hydralazine HCl
- 535 Methyl dopa
- 536 Reserpine

- 537 Trimethaphan Camsylate
  - 538 Pargyline
  - 530 Other Hypotensive Agents
- 4 *Vasodilating Agents*
- 541 Amyl Nitrate  
Isoamyl Nitrate
  - 542 Erythrityl Tetranitrate
  - 543 Isosorbide Dinitrate
  - 544 Pentaerythritol  
Tetranitrate
  - 545 Cycandelate
  - 546 Dipyridamole
  - 547 Isoxsuprine
  - 548 Nitroglycerin
  - 549 Papaverine HCl
  - 540 Other Vasodilating Agents
- 5 *Sclerosing Agents*
- 551 Sodium Tetradecyl Sulfate
  - 552 Other Sclerosing Agents
- 6 *Iron Supplements*
- 561 Ferrous Gluconate
  - 562 Ferrous Sulfate
  - 563 Iron Dextran
  - 560 Other Iron Supplements
- 7 *Anticoagulant*
- 571 Acenocoumarinol
  - 572 Bishydroxycoumarin
  - 573 Heparin Sodium
  - 574 Phenprocoumon
  - 575 Warfarin Sodium
  - 570 Other Anticoagulants
- 8 *Miscellaneous*
- 581 Protamine
  - 580 Other Miscellaneous
- VI Salts, Diuretics, Antigout**
- 1 *Sodium Salts*
- 611 Sodium Iodide
  - 612 Sodium Chloride
  - 613 Sodium Bicarbonate
  - 614 Sodium Lactate
  - 615 Sodium Citrate
  - 616 Sodium Sulfate
  - 610 Other Sodium Salts
- 2 *Calcium Salts*
- 621 Calcium Chloride
  - 622 Calcium Gluconate
  - 623 Calcium Lactate
  - 624 Calcium Phosphate
  - 620 Other Calcium Salts
- 3 *Miscellaneous Salts*
- 631 Potassium Chloride
  - 632 Potassium Citrate
  - 633 Ammonium Nitrate
  - 634 Magnesium Sulfate
  - 635 Potassium Bicarbonate
  - 630 Other Miscellaneous Salts
- 4 *Diuretics*
- 641 Chlormerodin
  - 642 Meralluride
  - 643 Mercaptomerin Sodium
  - 644 Merethoxylline
- 645 Mersalyl
  - 646 Acetazolamide
  - 647 Dichlorphenamide
  - 648 Ethoxzolamide
  - 649 Methazolamide
- 5 *Diuretics (thiazides)*
- 651 Hydrochlorothiazide
  - 652 Chlorothiazide
  - 653 Benzthiazide
  - 654 Hydroflumethiazide
  - 655 Bendroflumethiazide
  - 656 Cyclothiazide
  - 657 Methyclothiazide
  - 658 Trichlormethiazide
  - 659 Polythiazide
  - 650 Other thiazide diuretics
- 6 *Diuretics*
- 661 Furosemide
  - 662 Ethacrynic Acid
  - 663 Spironolactone
  - 664 Triamterene
  - 665 Mannitol
  - 666 Urea
  - 667 Chlorthalidone
  - 668 Metolazone
  - 669 Quinethazone
  - 660 Other Non-Thiazide Diuretics
- 7 *Antigout and Uricosuric Agents*
- 671 Allopurinol
  - 672 Colchicine
  - 673 Desacetylmethylcolchicine
  - 674 Probenecid
  - 675 Sulfinpyrazone
  - 670 Other Antigout and Uricosuric Agents
- VII Gastrointestinal and Spasmolytics**
- 1 *Antidiarrhea*
- 711 Diphenoxylate
  - 712 Kaolin
  - 713 Pectin
  - 710 Other Antidiarrheal Agents
- 2 *Antiflatuents, Antacids, Adsorbents, and Acidifiers*
- 721 Simethicone
  - 722 Dexpanthenol
  - 723 Peppermint
  - 724 Aluminum Antacids
  - 725 Dihydroxyaluminum Antacids
  - 726 Calcium Carbonate
  - 727 Magaldrate
  - 728 Glutamic Acid
  - 720 Other Antiflatuents, Antacids, Adsorbents, and Acidifiers
- 3 *Laxatives and Cathartics*
- 731 Bisacodyl
  - 732 Cascara Segrada
  - 733 Castor Oil
  - 734 Dioctyl Sodium Sulfosuccinate
  - 735 Glycerin
  - 736 Magnesium Citrate
- 737 Magnesium Hydroxide
  - 738 Mineral Oil
  - 739 Sodium Phosphate
- 4 *Laxatives and Cathartics*
- 741 Psyllium Hydrophilic Mucilloid
  - 742 Casanthranol
  - 743 Danthron
  - 744 Phenolphthalein
  - 745 Senna Extracts
  - 746 Enemas
  - 747 Methyl Cellulose
  - 740 Other Laxatives and Cathartics
- 5 *Antiemetics*
- 751 Tridihexethyl Chloride
  - 752 Trimethobenzamide
  - 753 Anisotropine Methylbromide
  - 754 Benzquinamide HCl
  - 755 Buclizine HCl
  - 756 Dipheamanil Methylsulfate
  - 757 Glycopyrrolate
  - 758 Diphenidol
  - 759 Thiethylperazine
  - 750 Antiemetics
- 6 *Emetics and Exchange Resins*
- 761 Apomorphine
  - 762 Ipecac
  - 763 Sodium Polystyrene Sulfonate
  - 764 Cholestyramine
  - 760 Other Emetics and Exchange Resins
- 7 *Digestive Enzymes and Digestants*
- 771 Pancrelipase
  - 772 Pepsin
  - 773 Pancreatin
  - 774 Taurocholic Acid
  - 775 Dehydrocholic Acid
  - 776 Pehnyltoloxamine Citrate
  - 777 Amylase (Amylolytic Enzymes)
  - 778 Chymotrypsin
  - 779 Trypsin
- 8 *Digestive Enzymes and Digestants*
- 781 Alpha-Chymotrypsin
  - 782 Hyaluronidase
  - 783 Streptokinase and Streptodornase
  - 784 Lipase
  - 785 Fibrinolysin
  - 786 Desoxyribonuclease
  - 780 Other Digestive Enzymes and Digestants
- 9 *Spasmolytics*
- 791 Aminophylline
  - 792 Dyphylline
  - 793 Hyoscyamus
  - 794 Oxtriphylline
  - 795 Theophylline
  - 790 Other Spasmolytics
- VIII Hormones**
- 1 *Antidiabetics and Insulins*
- 811 Chlorporpamide

- 812 Acetohexamide
  - 813 Tolbutamide
  - 814 Phenformin HCl
  - 815 Tolazamide
  - 816 Glucagon
  - 817 Insulin
  - 810 Other Antidiabetics and Insulins
- 2 *Oxytocics*
- 821 Ergonovine Maleate
  - 822 Methylergonovine Maleate
  - 823 Oxytocin
  - 824 Dynoprost
  - Tromethamine
  - 825 Other Oxytocics
- 3 *Thyroid, Antithyroid, and Parathyroid*
- 831 Thyroid (natural)
  - 832 Thyroglobulin
  - 833 Thyroid (synthetic)
  - 834 Propylthiouracil
  - 835 Methimazole
  - 836 Parathyroid
  - 837 Dihydrotachysterol
  - 830 Other Thyroid, Antithyroid, and Parathyroid Agents
- 4 *Androgens, Estrogens, and Progesterones*
- 841 Testosterone
  - 842 Methyltestosterone
  - 843 Fluoxymesterone
  - 844 Nethandrolone
  - 845 Norethandrolone
  - 846 Nandrolone Decanoate
  - 847 Estradiol
  - 848 Estrone
  - 849 Diethylstilbestrol
- 5 *Androgens, Estrogens, and Progesterones*
- 851 Conjugated and Esterified Estrogens
  - 852 Chlorotrianisene
  - 853 Dienestrol
  - 854 Progesterone
  - 855 Hydroxyprogesterone
  - 856 Dydrogesterone
  - 857 Ethisterone
  - 858 Lututrin
  - 859 Medoxyprogesterone
  - 850 Other Androgens, Estrogens, and Progesterones
- 6 *Adrenal Hormones*
- 861 Cortisone Acetate
  - 862 Betamethasone Valerate
  - 863 Disoxycorticosterone
  - 864 Dexamethasone
  - 865 Fludrocortisone
  - 866 Fluocinonide
  - 867 Fluocinolone
  - 868 Hydrocortisone
  - 869 Fluprednisolone
- 7 *Adrenal Hormones*
- 871 Meprednisone
  - 872 Methylprednisolone
  - 873 Prednisolone
  - 874 Paramethasone
  - 875 Prednisone
- 876 Triamcinolone
  - 877 ACTH
  - 870 Other Adrenal Hormones
- 8 *Contraceptives*
- 881 Mestranol
  - 882 Ethinyl Estradiol
  - 883 Norethynodrel
  - 884 Norethindrone
  - 885 Ethynodiol Diacetate
  - 886 D-Norgestrel
  - 887 Dimethisterone
  - 880 Other Contraceptives
- 9 *Miscellaneous Hormones*
- 891 Somatotrophic Hormone
  - 890 Other Miscellaneous Hormones
- IX Serums, Toxoids, Vaccines, Topical, Anaesthetics, Vitamins**
- 1 *Serums and Live Vaccines*
- 911 Horse Hyperimmune Serum
  - 912 Human Hyperimmune Serum
  - 913 Gamma Globulin
  - 914 Blood Fractions
  - 915 Rubiola
  - 916 Rubella
  - 917 Mumps
  - 918 Polio, Oral
  - 919 Small Pox, Vaccinia
  - 910 Other Serums and Live Vaccines
- 2 *Toxoids and Killed Vaccines*
- 921 Diphtheria
  - 922 Tetanus
  - 923 Cholera
  - 924 Influenza
  - 925 Pertussis
  - 926 Rabies
  - 927 Typhoid
  - 928 Typhus
  - 920 Other Toxoids and Killed Vaccines
- 3 *Topical*
- 931 Boric Acid
  - 932 Idoxuridine
  - 933 Potassium Nitrate
  - 934 Silver Nitrate
  - 935 Triethanolamine Polypeptide Oleate
  - 936 Mouthwashes, Gargles, Lozenges
  - 937 Hexachloraphene
- 4 *Topical*
- 941 Candididin
  - 942 Carbol-Fuchsin
  - 943 Gentian Violet
  - 944 Undecylenic Acid
  - 945 Gamma Benzene Hexachloride
  - 946 Crotamiton
  - 947 Iodine and Povidone Iodine
  - 948 Nitrofurazone
  - 949 Potassium Permanganate
  - 940 Other Topicals
- 5 *Topical*
- 951 Silver
- Sulfadiazine
  - 952 Thimerosal
  - 953 Aluminum Acetate
  - 954 Miconazole
  - 955 Phenylmercuric Acetate
  - 956 Other Astringents
  - 957 Other Vehicles
  - 958 Other Emollients
  - 959 Other Protectives
- 6 *Anaesthetics (general)*
- 961 Ether, Vinyl Ether
  - 962 Halothane
  - 963 Methoxyflurane
  - 964 Fluroxene
  - 965 Trichloroethylene
  - 966 Enflurane
  - 967 Cyclopropane
  - 968 Nitrous Oxide
  - 969 Ethylene
  - 960 Other Anaesthetics (general)
- 7 *Anaesthetics (local)*
- 971 Procaine
  - 972 Lidocaine
  - 973 Cetacaine
  - 974 Other "caine" derivatives
  - 975 Other "non-caine" local anaesthetics
- 8 *Vitamins*
- 981 Vitamin A
  - 982 Vitamin D
  - 983 Vitamin E
  - 984 Vitamin K
  - 985 Multivitamins
  - 986 Multivitamins with minerals
  - 987 Methionine
  - 980 Other Fat Soluble Vitamins
- 9 *Vitamins (water-soluble)*
- 991 Thiamine
  - 992 Riboflavin
  - 993 Nicotinic Acid
  - 994 Pyridoxine
  - 995 Cyanocobalamin
  - 996 Ascorbic Acid
  - 997 Pantothenic Acid
  - 998 Folic Acid
  - 990 Other Water-Soluble Vitamins
- O Miscellaneous**
- 1 *Diagnostic*
- 011 Dyes
  - 012 Iodides
  - 013 Radioisotopes
  - 014 Skin Tests
  - 015 Gastric Function
  - 010 Other Diagnostics
- 2 *Unclassified Therapeutic Agents*
- 021 Levodopa
  - 022 Clomephene
  - 023 Cromolyn Sodium
  - 024 Amantadine HCl
  - 025 Disulfiram

- 026 Potassium Perchlorate
- 027 Palidoxine
- 028 Sodium Benzoate
- 029 Benzoic Acid
- 020 Other Unclassified  
Therapeutic Agents

### 3 Miscellaneous

- 031 Activated Charcoal
- 032 Penicillamine
- 033 Dimercaprol
- 034 Deferoxamine Mesylate
- 035 Edetate Calcium  
Disodium
- 036 Ethanol
- 037 Dextrose
- 038 Placebo
- 039 Chlorophyll
- 030 Other Miscellaneous

tient, are all assembled in the computer at the University of Maine. It is thus possible to record the diagnoses, procedures, and medications of each resident and faculty person. Thus, the frequency incidence of diagnoses dealt with, the frequency and pattern of drug usage, and the procedures done can be analyzed for each individual and for the group. The availability of the data in this form should be very useful for studying such problems as result of therapy, sequelae to using drugs and combination of drugs, drug interactions, and the long-term followup of drug-related problems. The computer program has been written to allow such studies in addition to its basic design for recording, analyzing, and making available for audit the diagnoses made, procedures done, and prescribing habits of the residents and faculty. The computer program is written in P.L. 1 and is available for anyone who wishes to use it.

Although the Richards Drug Classification was designed for a specific purpose, the authors were aware of its potential for multiple other uses. An attempt was made to make it as universal as possible.

All generic or single drugs were given an identification number with only rare exceptions. A few drugs such as natural thyroid extract, conjugated estrogens, digitalis leaf, and tincture of Belladonna are obviously mixtures of active ingredients, but are necessarily dealt with as if they were a single entity. The drugs which are produced separately and then added together were kept separate except for multi vitamins which were lumped together for convenience's sake. In using the drug code, a drug such as Donnatal® would require two code numbers to identify the two active ingredients. This system

is working very well for the purpose for which it is designed.

We are aware that there may be omissions or inaccuracies in the drug code. We invite anyone interested in using the code to forward to us any suggestions for improving the Richards Drug Classification. It is our sincere hope that it will prove a useful tool in many areas of drug study and medical audit.

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## Use and Abuse of Laxatives

ROBERT G. PIETRUSKO, Pharm.D.

### ABSTRACT

Dietary change and attention to proper bowel habits are frequently the only therapy necessary for the treatment of constipation. When laxative intervention is necessary, one of the milder agents should be employed over a short period of time. Chronic abuse of stimulant cathartics, often deeply rooted in family or ethnic traditions, is a significant problem and difficult to treat.

High fiber diets and bulk laxatives have shown great promise in the treatment of diverticulitis. Long-term studies are needed to confirm the possibility that chronic use of bulk-creating substances prevents colonic cancer.

Recent findings provide new insight into the mechanism of action of laxatives. Surfactants produce effects similar to those of irritant cathartics. Surfactants may also increase absorption of other drugs and possibly increase their toxic potential.

Enemas are useful for thorough cleansing of the distal bowel and for alleviating fecal impaction. Suppositories, although probably not as effective as enemas, are more convenient for nurses and patients.

### INTRODUCTION

Self-purgation is a ritual performed by much of the population.<sup>1,2</sup> Advertising encourages this practice by making people feel "guilty" about constipation and by portraying the daily bowel movements as the secret to a healthy and happy life. Well over 200 million dollars are spent yearly for over-the-counter laxatives.<sup>3</sup>

Constipation is defined as an infrequent or difficult passage of feces. By this definition, most of humanity can claim to be constipated at some time. Constipation may be more strictly defined as a decrease in frequency of bowel movements, accompanied by a prolonged and difficult passage of stool, followed by a sensation of incomplete evacuation.<sup>4</sup>

The normal frequency of bowel movements varies widely. A British study of 1,455 patients re-

vealed that over 98% had bowel movements in the range of three per week to three per day,<sup>5</sup> but even once weekly bowel movements are not necessarily abnormal.

Erroneous concepts concerning constipation still prevail. Many persons use laxatives because they believe toxic substances may be absorbed into the body without a daily bowel movement, or because they believe that weakness and headaches are due to constipation. Cathartics are also used for the treatment of the common cold, depression, anger, earache and other ailments. The practice of administering laxatives for abdominal cramps and pain is particularly dangerous. Another common misconception is that over-the-counter medication is totally safe and without adverse effect. If a bowel movement is induced by a laxative, it may be several days before enough stool is present for another bowel movement. Therefore, when an individual attempts to maintain a daily bowel movement with the prolonged use of laxatives, a vicious cycle may develop in which either more of the same laxative or a more potent one must be used. When this process results in frequent and prolonged use of irritant cathartics, development of a "cathartic colon" is likely (Figure 1). Over 90% of patients suffering from chronic ill health due to laxative abuse are women, many of whom are in the health professions.<sup>2</sup> Diagnosis of cathartic colon and other disorders arising out of laxative abuse is often notoriously difficult since patients frequently do not volunteer information concerning chronic laxative ingestion or may flatly deny such use.<sup>6-9</sup>

### COLON PHYSIOLOGY

Normal activity in the colon involves mixing and propulsive movements. The mixing movements cause segmentation of the lumen which thoroughly exposes the colonic contents to the surface of the large intestine. Mass movement, a form of propulsion, causes the fecal material to move towards the anus. Meals seem to stimulate propulsive movement, also known as the duodenocolic or gastrocolic reflex. The hormone gastrin may play a role, but this is probably only one small factor. A complex interplay of other hormones, sympathetic and parasympathetic innervation, local neuronal effects, and central nervous system integration also influences propulsive movements.<sup>10</sup>

The mechanism for evacuation of fecal material is as follows:

(1) Defecation reflex — Feces enter the rectum

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Fig. 1. Cathartic Colon. The patient is a 69-year-old white male who complained of dysuria and constipation. Chronic laxative use was denied, but later his wife stated that he indeed was abusing laxatives for many years. There were no other medical problems except benign prostatic hypertrophy.

Radiologic changes are usually first seen in the cecal region and the right side of the colon is predominantly affected.

and wall distension results. Peristalsis is initiated by the myenteric plexus, which is located in the intestinal mucosa. This is an extremely weak reflex.

(2) Sacral spinal cord innervation — Afferent fiber stimulation of the sacral area of the spinal cord causes a reflex parasympathetic impulse that intensifies peristaltic waves, relaxes the internal anal sphincter, and promotes a Valsalva maneuver.

(3) Voluntary relaxation of the external anal sphincter — This relaxation causes the fecal mass to be expelled. Voluntary contraction of the sphincter prevents defecation. The defecation reflex usually dies out after a few minutes and usually will not return for many hours thereafter.<sup>11</sup>

When constipation occurs, mean colonic transit time is significantly slowed. However, gastric emptying rates and small intestinal transit times are the same in patients with constipation or diarrhea.<sup>12</sup>

#### CAUSES OF CONSTIPATION

The most common cause of constipation is failure to heed "the urge to go." When this defecation reflex is ignored frequently, severe constipation develops. This non-organic condition is the one most likely to precipitate laxative abuse. Many

TABLE 1

MAJOR CAUSES OF CONSTIPATION	
<i>Mechanical</i>	<i>Medications</i>
Carcinoma	Aluminum containing antacids
Defective electrolyte transfer	Anticholinergics
Diverticulosis	Calcium carbonate
Fissures	Ganglionic blocking agents
Hemorrhoids	Iron salts
Hirschprung's disease	Laxatives (when abused)
Neurological diseases	Opiates
Strictures	Phenothiazines
Tumors	Sedatives
Ulcers	Tricyclic antidepressants
<i>Physiological</i>	<i>Psychological</i>
Dehydration	Avoidance of "urge to go"
Insufficient bulk	Depression
Starvation	Emotional stress
<i>Systemic</i>	<i>Other</i>
Hypercalcemia	Decreased physical activity
Hyperparathyroidism	Lead poisoning
Hypokalemia	Obesity
Hypothyroidism	Old age
Porphyria	Pregnancy

other factors can contribute to causing constipation (Table 1).

#### AN APPROACH TO MANAGEMENT

Psychological influences cannot be ignored. In a double-blind study of 20 patients with chronic constipation, 14 obtained relief with the use of a placebo.<sup>13</sup> Discussion and treatment of psychological problems may be all the treatment that is necessary. Temporary constipation may accompany stressful situations such as moving, travel, or change of employment.<sup>14</sup> Several doses of a mild laxative may be of some benefit.

Anyone who presents with true constipation should have a complete workup to seek an organic etiology. Treatment of underlying disease will frequently cure constipation. If a mechanical problem is the cause, surgical or medical intervention will often alleviate it. Ulcerations, fissures, hemorrhoids, and inflammatory bowel disease are best treated with specific therapies, although short-term adjunctive treatment with a mild laxative may occasionally be helpful. Diverticulosis is best approached with a high-residue diet or bulk-forming laxatives. In patients with stricture of the colon, bulk laxatives should not be used since they may cause impaction proximal to the stricture. Emollients or stool softener surfactants are the best agents to use in this condition.<sup>14-16</sup> Fecal impaction is treated by manual disimpaction, followed by a phosphate enema. Stool softeners or mild saline laxatives may be required for a period of time after the impaction has cleared.

For infants less than two months old, constipation is usually treated with sugars,<sup>17</sup> such as brown sugar or malt soup. These sugars ferment in the gut and distend the rectum via osmotic forces. Since constipation in the young child is commonly due to lack of bulk, dietary changes are usually necessary.

If these measures are ineffective, mild oral laxatives should be employed. When these are unsuccessful, suppositories should be tried; as a last resort, phosphate enemas can be used.<sup>18</sup>

Post partum constipation is common and can be particularly distressing since many factors prevent normal defecation. Restricted diet after delivery, dehydration, voluntary avoidance of defecation because of apprehension, episiotomy pain, hemorrhoids and fissures, and use of narcotic analgesics are some causes.<sup>19</sup> A mild laxative such as milk of magnesia is helpful. Irritant cathartics are sometimes used to initiate a bowel movement, but some of these agents are secreted into breast milk and can cause diarrhea in the newborn.

Laxatives are contraindicated when abdominal pain, nausea, vomiting or other symptoms of appendicitis are present.

When used properly, cathartics are relatively free of adverse effect. Side effects, other than diarrhea, occur in less than 1% of recipients.<sup>20</sup>

### INDIVIDUAL AGENTS

The term laxative suggests the elimination of a soft, formed stool, whereas a cathartic implies a more fluid evacuation.<sup>21</sup> Purgative denotes a more severe irritating action upon the bowel with cramping and electrolyte loss. This discussion will use the terms laxative and cathartic interchangeably, whereas purgative will pertain to the use of large doses of irritant cathartics. Although some clinicians do not consider evacuant enemas and suppositories to be laxatives, they are classified as such for the purposes of this review.

Many laxatives produce their effects by mechanisms other than those commonly described in standard pharmacology texts<sup>22</sup> (Table 3). Active fluid and electrolyte secretion may be common to all laxatives. The extent of this active process probably differs with each agent. To avoid confusion, the traditional classification of laxatives is used below.

#### *Bulk-Forming Laxatives*

The latest food fad is a diet containing large amounts of fiber residue in the form of raw milled bran. Unlike many dietary fads, this diet is based upon scientific studies that link the low fiber content of the usual Western diet with an increased risk of colonic cancer and diverticulosis.<sup>23-25</sup> Crude fiber in the average diet in industrialized countries averages 4 grams per day, compared to 30 grams in non-industrialized nations.<sup>26</sup> A simple change in diet or the ingestion of a bulk laxative might prevent colonic cancer or diverticulosis; the latter is probably the most common disorder of the large intestine.

Bulk laxatives include methylcellulose, sodium carboxymethylcellulose, psyllium preparations, karaya gum (sterculia), dietary bran, and malt soup extract. Their laxative effect is due to absorption

and retention of large amounts of water, sometimes as much as twenty times the weight of the ingested material, causing hydration of the stool.<sup>27</sup> The mechanical distension caused by the laxative also promotes peristalsis and facilitates passage of the stool. The laxative effect is usually seen within 12 to 24 hours of ingestion, but may take up to three days.

Bulk cathartics are relatively safe, since they are not absorbed systemically and resemble a high fiber diet. As initial therapy for constipation, these products are an excellent choice. They have been shown effective in constipated post partum and elderly patients, chronic laxative abusers, and patients with irritable bowel syndrome or diverticular disease; they are also useful in preparing patients for barium enema examinations.<sup>28-31</sup>

Whether bulk ingestion can prevent colon cancer has not yet been established.<sup>32</sup> Low residue diets can cause hypertrophy of the bowel musculature with resultant increase of intracolonic pressure which favors the development and progression of diverticulosis.<sup>33</sup> Bulk decreases rectosigmoid pressure and therefore is useful for treating diseases in this location. Brodribb and Humphreys<sup>34</sup> have shown that ingestion of bulk improved the status of 82% of their patients, and suggested that this form of therapy may prevent diverticulosis. Bulk laxatives have been advocated for weight reduction, but they are probably not particularly useful for this purpose.<sup>35</sup>

The particular choice of bulk laxative is relatively unimportant.<sup>14</sup> Karaya gum, derived from the bark of the steruliaca family of trees, and psyllium, obtained from the seeds of the *Plantago* plant, have proven laxative effects.<sup>36-38</sup> The synthetic colloidal materials, including methylcellulose and sodium carboxymethylcellulose, have a high degree of uniformity and can be readily compressed into tablets. Malt soup extract, obtained from barley containing amylolytic enzymes, contains maltose, protein, and potassium. This agent reduces fecal pH, which may contribute to its action.<sup>39</sup> Due to its relative safety, malt soup extract can be administered to infants less than two months of age.<sup>17</sup>

Cass and Wolf<sup>40</sup> reported that psyllium seed preparations were considerably more effective than methylcellulose, milk of magnesia, mineral oil, cascara, or phenolphthalein; however, their study was not double-blind. Berberian et al<sup>41</sup> compared a combination of methylcellulose and psyllium to plain methylcellulose. The combination proved superior, but no comparison was made to plain psyllium. Cass and Frederik<sup>42</sup> later compared methylcellulose to a combination of caroid and bile salts and phenolphthalein. Both regimens produced a significant and adequate laxative effect although the irritant cathartic had a more rapid onset and was more uniformly effective.

Side effects are relatively rare with the bulk laxatives. Minor adverse effects include frequent flatulence, borborygmi, and defecation of soft, bulky

TABLE 2

SOME PROPRIETARY LAXATIVE PRODUCTS COMPONENTS			
LAXATIVE	Diethyl Sodium		
	Phenolphthalein	Sulfosuccinate	Other
Agoral®	+		Mineral oil
Alophen	+		Aloin
Caroid and bile salts with phenolphthalein	+		Cascara sagrada
Carter's Little Pills			Aloe Podophyllum
Colace®		+	
Correctol	+	+	
Dialose®		+	Sodium carboxymethylcellulose
Dialose® Plus		+	Sodium carboxymethylcellulose Casanthranol
Dorbane®			Danthron
Dorbantyl®		+	Danthron
Doxidan®			Danthron
			Diethyl calcium sulfosuccinate
Doxinate®		+	
Dulcolax®			Bisacodyl
Espotabs	+		
Evac-U-Gen®	+		
Ex-Lax	+		
Feen-A-Mint	+		
Fleet® Enema			Sodium phosphate Sodium biphosphate
Fleet Phosph Soda			Sodium phosphate Sodium biphosphate
Fletcher's Castoria			Senna
Haley's M-O®			Mineral oil Magnesium hydroxide
Konsyl			Psyllium
LA Formula			Psyllium
Malt Supex			Malt soup extract
Metamucil®			Psyllium
Modane®			Danthron
Mucilose			Psyllium
Peri-Colace®		+	Casanthranol
Petrogalar			Mineral oil
Phenolax	+		
Sal Hepatica			Sodium biphosphate
Senokot®			Senna
Serutan			Psyllium
			Methylcellulose
Surfak®			Diethyl calcium sulfosuccinate
Vacuetts®			Sodium biphosphate Sodium bicarbonate
X-Prep®			Senna

stools.<sup>32</sup> Esophageal, gastric, small intestinal, and colonic obstructions have been reported; either poor intake of water or impaired gastrointestinal function accompanied these effects.<sup>43</sup> Allergic-type reactions to the vegetable and plant derivatives have been reported.<sup>44,45</sup>

Psyllium does not interfere with the absorption of sodium warfarin.<sup>46</sup> The clinical significance of binding with other drugs is unclear. A slight but statistically significant increase of bile salt excretion occurs.<sup>7</sup> With constant ingestion, the serum cholesterol level may be decreased.

Patients should be carefully instructed to mix bulk laxatives with water and/or to drink a generous quantity of fluid, at least 8 ounces. They should not chew or swallow tablets without water. Relative contraindications include complete or partial intestinal obstruction, or disabling adhesions. Table 2 lists examples of bulk laxatives and other agents.

They are also frequently combined with an irritant or wetting agent.

#### *Stimulant Cathartics*

Stimulant cathartics are useful for acute constipation, such as that which is caused by other drugs and is refractory to milder laxatives; constipation due to prolonged bedrest or hospitalization; constipation stemming from poor dietary habits; and preparation for x-ray examination of the abdomen, especially for barium enema.<sup>47</sup> The term stimulant may be misleading since these laxatives have mechanisms of action other than mere contact.<sup>22,48</sup> Originally it was thought that they stimulated peristalsis only by direct contact with the mucosa or by stimulation of the myenteric plexus.

This group of laxatives can induce anything from a relatively mild laxative action to a severe purging with resultant electrolyte imbalance and dehydra-

TABLE 3

PHARMACOLOGIC SUMMARY OF COMMONLY USED LAXATIVES					
LAXATIVE	Usual Adult Dose	Onset of Action	Site of Action	Probable Mechanism of Action	Systemic Absorption
<i>Bulk Laxatives</i>					
Methylcellulose	4 to 6 gm	12 to 24 hours (may take up to 3 days)	Small and large intestine	Mechanical distension	No
Psyllium	7 gm	12 to 24 hours (may take up to 3 days)	Small and large intestine	Mechanical distension	No
<i>Saline Laxatives</i>					
Magnesium and sodium sulfates	15 gm	½ to 3 hours	Small and large intestine	Release of cholecystokinin Osmotic action	Yes
Magnesium citrate	200 ml	½ to 3 hours	Small and large intestine	Release of cholecystokinin Osmotic action	Yes
Sodium and potassium tartrates and phosphates	10 gm	½ to 3 hours	Small and large intestine	Osmotic action	Yes
<i>Stimulant Laxatives</i>					
Castor oil	15 to 30 ml	3 hours	Small intestine	Decreased contraction of circular smooth muscle of the small intestine Water and electrolyte secretion Stimulation of myenteric plexus	Yes
Cascara sagrada fluid extract	1 ml	6 to 12 hours	Colon	Direct stimulant activity Water and electrolyte secretion Stimulation of myenteric plexus	Yes
Senna	2 ml	6 to 12 hours	Colon	Direct stimulant activity Water and electrolyte secretion Stimulation of myenteric plexus	Yes
Danthron	75 mg	6 to 12 hours	Colon	Direct stimulant activity Water and electrolyte secretion Stimulation of myenteric plexus	Yes
Aloe	250 mg	6 to 12 hours	Colon	Direct stimulant activity Water and electrolyte secretion Stimulation of myenteric plexus	Yes
Bisacodyl	10 mg	6 to 12 hours	Colon	Direct stimulant activity Water and electrolyte secretion Stimulation of mucosal nerve plexus in the colon	Yes
Phenolphthalein	60 mg	6 to 12 hours	Colon	Water and electrolyte secretion Decreased glucose absorption Stimulation of mucosal nerve plexus in the colon Water and electrolyte secretion Decreased glucose absorption	Yes
<i>Hyperosmotic Laxatives</i>					
Glycerin	3 gm	30 minutes	Colon	Hygroscopic Local irritant effect	Yes
Sorbitol	120 ml	30 minutes	Colon	Hygroscopic	Yes (minimal amount)
<i>Surfactants</i>					
Diocetyl sodium and calcium sulfosuccinates	50 to 500 mg	24 to 48 hours	Colon	Detergent effect Water and electrolyte secretion	Yes
<i>Emollients</i>					
Mineral oil	15 to 30 ml	6 to 8 hours	Colon	Retards water absorption from the stool	Yes (minimal amount)

tion. If the dose is large enough, any of these agents is capable of inducing severe cramping and excessive fluid loss. Possible side effects of all stimulant laxatives include hypokalemia, enteric loss of protein, and malabsorption.<sup>7,49,50</sup>

Of all the laxatives, stimulant cathartics are the most abused by the public. Chronic abuse can lead to "cathartic colon" — a poorly functioning large intestine requiring extensive bowel retraining. The "cathartic colon" resembles chronic ulcerative colitis both radiologically and pathologically.<sup>51</sup>

This large group is subdivided into the following categories: 1) castor oil, 2) anthraquinones, and 3) diphenylmethanes.<sup>21</sup> Agents within each category closely resemble each other.

*Castor oil.* This disagreeable compound must first be hydrolyzed by lipase enzymes to produce the active ingredient, ricinoleic acid, which is active predominantly in the small intestine and thus requires only about three hours to initiate thorough evacuation of the bowel. Some ricinoleic acid is absorbed, but is metabolized like other fatty acids.<sup>52</sup> The laxative effect appears to be caused by a decreased contractile activity of circular smooth muscle of the small intestine, which speeds up movement of fecal material. Ricinoleic acid may also stimulate water and electrolyte secretion. There is no evidence for stimulant or irritant action.<sup>53</sup> With the use of scanning electron microscopy, it has been shown that ricinoleic acid causes

erosion of intestinal villi and disorganization of the microvillus surface.<sup>54</sup> Long-term use of castor oil can lead to malabsorption of nutrients by this mechanism. To mask the disagreeable oily taste of castor oil, various emulsified preparations have been made available.

**Anthraquinones.** This group of compounds includes senna, cascara sagrada, danthron, and aloe. With the exception of danthron, which is a free anthraquinone, these agents are glycoside derivatives of 1,8-dihydroxyanthraquinone. These laxatives pass mostly unchanged through the small intestine to the colon where they are hydrolyzed by bacterial enzymes into active free aglycones. A portion of the dose is absorbed and subsequently acts on the colon.<sup>55</sup> Their exact mechanism of action is unknown; direct stimulant activity, stimulation of the myenteric plexus, and altered sodium transport may be involved.<sup>56</sup> Since their action is mainly limited to the colon, the onset of action is from six to twelve hours. Effectiveness is fairly uniform with this group of laxatives since they are so potent.<sup>57,58</sup> As a result of systemic absorption, a certain amount appears in the urine, giving it a pink to red color.<sup>59</sup> This may give false-positive tests for urobilinogen and elevated estrogens by the Kober reaction.<sup>60,61</sup> These laxatives also cross into breast milk in sufficient quantity to induce catharsis in the infant.<sup>28,62</sup> Melanosis coli, a darkened pigmentation of the colonic mucosa, has been observed in chronic users of these laxatives.<sup>8,63,64</sup> Danthron, in combination with dioctyl sodium sulfosuccinate, has produced at least one case of hepatitis.<sup>65</sup> It is possible that the surfactant caused increased absorption of danthron. Aloe, present in Carter's Little Pills and Alophen, has the reputation of being the most irritating of these laxatives.

**Diphenylmethanes.** These stimulant cathartics include bisacodyl and phenolphthalein, both of which supposedly act directly on the mucosal nerve plexus of the colon. Other possible mechanisms include inhibition of sodium-potassium ATPase and glucose absorption.<sup>56,66</sup>

Bisacodyl, chemically related to phenolphthalein, has been called a "contact" cathartic since its effect can be overcome with the application of a local anesthetic. Small intestinal function is not affected; therefore, after oral administration the onset of action ranges from six to eight hours. When administered orally, only about 5% is absorbed. No systemic toxicity has yet been reported. A unique advantage of this laxative is that it can also be administered rectally. The suppository takes fifteen minutes to one hour to produce its effects. The tablets and suppository have been used in combination to cleanse the colon prior to barium enema.<sup>67</sup> Occasionally suppositories cause a rectal burning sensation. Side effects stem mainly from excessive purgation, and include metabolic acidosis or alkalosis, muscle weakness, hypokalemia, tetany, and protein-losing enteropathy.<sup>68</sup> Antacids should not be administered with bisacodyl, since an increase

in gastric pH will cause a dissolution of the enteric coating of the tablet, leading to abdominal cramping and vomiting.<sup>69</sup> Obviously these tablets should not be chewed.

Two forms of phenolphthalein are available — white and yellow. Yellow phenolphthalein is generally two or three times more potent than the purified white form. Like bisacodyl, phenolphthalein acts primarily on the colon.<sup>70</sup> Up to 15% of the drug is absorbed systemically and undergoes enterohepatic circulation. For this reason, the onset of action is six to eight hours, but the cathartic effect may last for up to three to four days. Bile must be present for phenolphthalein to produce its effect.<sup>71</sup> Part of the absorbed medication is excreted into the urine. If the urine is alkaline, phenolphthalein will produce a pink to red color. In a similar fashion, a soap suds enema will produce a red stool in the presence of phenolphthalein. When used for short periods of time, phenolphthalein is relatively nontoxic. Occasionally, excessive purgation occurs. Prolonged use has led to many problems. Osteomalacia secondary to impaired absorption of vitamin D and calcium has been reported occasionally.<sup>68,72,73</sup> Phenolphthalein abuse can mimic Bartter's syndrome by inducing hyperaldosteronism and hypokalemia.<sup>74</sup> Protein-losing gastroenteropathy and factitious diarrhea have also been reported.<sup>9,68</sup> Certain individuals manifest a skin hypersensitivity to phenolphthalein in the form of a fixed drug eruption;<sup>75-77</sup> deaths can occur upon repeat exposure in these individuals. Other dermal toxicities include toxic epidermal necrolysis and bullous skin reactions in the presence of sunlight.<sup>78,79</sup> By interfering with both acid and enzyme hydrolysis of estriol conjugates in the urine, it can cause a decrease in urinary estriol values without a decline in fetal well-being.<sup>80</sup>

Oxyphenisatin was formerly a member of this group of laxatives. It was commonly combined with dioctyl sodium sulfosuccinate in combination products which reportedly caused several cases of hepatitis.<sup>81-83</sup> This hepatotoxicity closely resembles chronic active hepatitis.<sup>84</sup> The surfactant stool softener was thought to have increased the absorption of oxyphenisatin, producing a critical concentration in liver parenchyma.<sup>85</sup> Oxyphenisatin has been removed from the United States market.

Other members of this group of laxatives are very irritating and therefore should not be used in the treatment of constipation. Jalap, ipomea, calomel, podophyllum, colocynth, elaterin, and gamboge are examples. In addition to being caustic, mercurous chloride (calomel) when used chronically has been implicated in causing mercury poisoning.<sup>86</sup> Podophyllum is teratogenic and may cause fetal death.<sup>87</sup> Prune powder and concentrate have not been proven to be of benefit when used alone and have not been found to contain any "stimulant" ingredients.

#### *Saline Laxatives*

Magnesium, sulfate, phosphate, and tartrate are

ions that have been used to treat constipation for hundreds of years. Traditional teaching dictates that hypertonic salts attract and retain a large volume of isotonic fluid in the stomach, thus stimulating peristalsis in the small intestine, reducing transit time and causing the passage of a watery stool. Osmotic forces were thought to be the only way in which catharsis was induced. More recent findings suggest that saline cathartics stimulate the release of cholecystokinin,<sup>88-90</sup> stimulating small bowel motility and inhibiting absorption of fluid and electrolytes from the jejunum and ileum.<sup>91</sup> Some combination of osmotic activity together with cholecystokinin release probably accounts for the cathartic effects of saline laxatives. Because of the osmotic activity of these substances, the patient should be advised to take them with at least a full glass of water so that no net fluid loss occurs. Without adequate fluid replacement, saline cathartics can produce dehydration.

The sulfate salts are considered to be the most potent of this group of laxatives, followed by magnesium salts. Phosphates and tartrates are the weakest. Upon oral administration of a saline cathartic, laxation occurs in three to six hours in most patients, but it may occur within an hour in some. Rectal administration has more rapid action.

Magnesium hydroxide is a mild, fairly good tasting saline cathartic. Milk of magnesia contains 7 to 8.5% magnesium hydroxide in suspension. Magnesium citrate solution is more pleasant tasting. Most commercial preparations contain the equivalent of 3.1 to 3.8 grams of magnesium oxide in 200 ml of effervescent solution. Magnesium citrate solutions should be kept refrigerated to retain potency and palatability. Magnesium sulfate and sodium sulfate are fairly potent cathartics. Because of their bitter taste, they are not commonly utilized in commercial products. Administration with lemon juice often will overcome the bitter taste. Their main value is in treating poisonings.<sup>92</sup>

About 20% of the magnesium contained in magnesium salts is absorbed. In normal individuals the magnesium is rapidly cleared by the kidneys. However, in patients with renal impairment, serum magnesium levels may rise to toxic levels and cause central nervous system depression, hypotension,<sup>93</sup> muscle weakness and electrocardiographic changes. For these reasons, magnesium laxatives are contraindicated in renal failure.

Phosphate salts are available both in oral and rectal forms; oral solutions are pleasant tasting. The normal laxative dose contains 96.5 mEq of sodium, therefore it should be administered cautiously to patients on a low sodium diet. Prolonged use or overdose of this product in young children has resulted in death.<sup>94-96</sup> Rectal preparations (e.g., Fleet's Enema) work within approximately five minutes, and act by causing distension and by osmotic activity. Depending upon bowel function, up to 10% or more of its sodium content (about 4.4

grams) may be absorbed. Barium enema preparation and elimination of fecal impactions are two clinical implications for the use of phosphate enemas. The use of phosphate salts in children under two years of age, or in patients with Hirschsprung's disease, renal impairment, megacolon, or imperforate anus may produce complications including hypocalcemia, tetany, hypernatremic dehydration, and hyperphosphatemia.<sup>97-99</sup>

#### *Hyperosmotic Laxatives*

This category includes glycerin and sorbitol. Glycerin in the form of a suppository, usually produces a bowel movement within thirty minutes. Rectal irritation can occur with its use. A small amount of glycerin can also be used as an enema. This trihydroxy alcohol produces its effect via a hygroscopic action and local irritant effects.<sup>100,101</sup> Oral glycerin is ineffective since it is rapidly absorbed and metabolized. Sorbitol is a relatively non-irritating poly-alcohol derivative of sorbose. In contrast to glycerin it is very poorly absorbed and therefore can be administered orally. Sorbitol is commonly used to counteract the constipating effects of sodium polystyrene sulfonate (Kayexalate®).

#### *Surfactant Laxatives*

The dioctyl sulfosuccinates are anionic surface active agents which have detergent activity. They lower surface tension at the oil-water interface of the stool, thereby allowing the fecal material to be penetrated by water and fat. Recent findings suggest that in addition to acting directly on the stool, these drugs might change intestinal morphology and interfere with cellular function. They also appear to cause fluid and electrolyte accumulation in the colon.<sup>102,103</sup>

Surfactant laxatives are useful for conditions in which straining at defecation should be avoided, such as after myocardial infarction and rectal surgery; diseases of the rectum and anus which make passage of a firm stool difficult; for fecal impaction; and for post partum constipation.<sup>104-106</sup> They act within 24 to 48 hours. As prophylactic agents they appear to be of little value in preventing constipation.<sup>107,108</sup> Sodium and calcium salts are available for oral use. Not enough sodium or calcium is contained in these products to be of clinical concern. Fecal impactions can be softened and eliminated within several hours after the use of the rectal preparation containing the potassium salt.<sup>104</sup> Poloxalkol is an oral tasteless "nonionic" surfactant with similar wetting properties. This agent begins to act only after three to five days.

Other than a bitter taste from the liquid form and occasional diarrhea, side effects from surfactants seem to be rather uncommon. Older pharmacological data suggested that surfactants were not absorbed and that they were relatively harmless. Systemic absorption does occur with subsequent

excretion in the bile. Surfactants have been implicated as a cause of chronic active hepatitis when used in conjunction with oxyphenisatin, as discussed above.<sup>85</sup> By facilitating absorption of other poorly absorbed substances, such as danthron and mineral oil, the surfactants may increase their clinical toxicity.<sup>85,109,110</sup> Greater mucosal damage is seen when aspirin and the surfactants are administered together than when each is given alone.<sup>111</sup> When sodium lauryl sulfate, another surfactant, is combined with erythromycin propionate, the resulting estolate salt is hepatotoxic.<sup>112</sup> Since surfactants produce a temporary change in intestinal permeability lasting a few hours, drugs that have a low therapeutic index probably should not be administered at the same time as the dioctyl sulfosuccinates.<sup>113</sup>

Combinations of stimulant cathartics and/or bulk forming agents with dioctyl sulfosuccinates are prevalent today. Well-controlled studies are needed to compare the combination products with their individual components.<sup>21</sup>

### *Emollient Laxatives*

Mineral oil (liquid petrolatum) is a mixture of poorly absorbable hydrocarbons derived from petroleum. It softens fecal materials by retarding absorption of water. The onset of action is about six to eight hours. Indications for mineral oil use include those conditions in which straining at defecation is to be avoided, e.g., abdominal surgery, hernia, aneurysm, stroke, myocardial infarction, and possibly hemorrhoidectomy. Becker<sup>114</sup> has argued that the need for mineral oil rarely outweighs its potential dangers, such as slowing of the healing process and increased risk of anorectal infections. Mineral oil can be administered either orally or rectally. Emulsified products are used to increase palatability and for better wetting properties, but in this form 35 to 60% of the mineral oil may be absorbed through the bowel wall. Non-emulsified mineral oil is absorbed only to a slight extent. Olive oil is sometimes included in this category. A large dose must be given since most of the olive oil is absorbed systemically.

Pruritis ani and anal leakage are minor annoying side effects which may occur during short-term use. Most of the problems associated with mineral oil result from chronic ingestion. Mineral oil is a lipid solvent and, as such, decreases absorption of food and the fat soluble vitamins A, D, E, and K.<sup>115,116</sup> Administration with meals should be avoided. Lipid pneumonitis can occur with oral ingestion particularly if taken at bedtime. The young, the elderly and the debilitated are more susceptible to this syndrome. Aspiration can produce acute or chronic pneumonitis or a localized granuloma simulating a neoplasm.<sup>117-119</sup> Mineral oil is carcinogenic in some strains of mice, and it may also indirectly induce cancer in man by the production of pulmonary fibrosis.<sup>120,121</sup> When this agent is absorbed, foreign body reactions can occur in the

mesenteric lymph nodes, the liver, and the spleen.

Mineral oil is contraindicated in the pregnant patient since it can decrease the availability of vitamin K to the fetus, and it may be carcinogenic. Severely debilitated individuals and those taking oral anticoagulants should not receive mineral oil. As mentioned previously, it should not be administered with dioctyl sulfosuccinates.

### *Enemas*

Clinical indications for enemas include surgery, delivery, lower bowel constipation, fecal impaction, and barium enema preparation. If administered properly, they will cleanse the distal colon by distension.<sup>122</sup> The most common reason for failure of an enema is improper administration. A cross-over study showed that in healthy individuals phosphate enemas were more efficient and effective than tap water, soap suds, or saline enemas.<sup>123</sup>

Proper preparation for barium enema radiologic examination is important, since a clear x-ray picture of the colon is most important in the early diagnosis of colonic cancer. Proper preparation should result in clean colons in over 95% of the patients on the first examination.<sup>124</sup> A survey of 74 institutions revealed that castor oil (most frequently employed) or another irritant cathartic was used in conjunction with a tap water, soap suds, or saline enema.<sup>125</sup> An alternative to the use of enemas is the hydration method,<sup>126</sup> which uses magnesium citrate along with oral and rectal bisacodyl. Saline lavage may improve patient acceptance and comfort,<sup>127</sup> but poor success, limited indications, the need to ingest six liters of fluid, and poor taste are negative aspects of this technique.<sup>124,128</sup> Good preparation requires that the laxatives employed work in both small and large bowel. The small intestine can be stimulated by magnesium salts, phosphates, or castor oil. Colon stimulation is generally achieved with bisacodyl, senna, or cleansing enemas.

### *Suppositories*

Suppositories are useful for evacuating the lower bowel. Claims have been made that suppositories may be equal in effectiveness to enemas.<sup>126,129</sup> The use of suppositories requires less nursing time and is aesthetically more pleasing to the patient. One drawback, however, is that suppositories are not very effective if hard, dry stool is present.<sup>100</sup> Various products have been discussed under their respective classifications. One preparation not previously mentioned is a suppository containing sodium biphosphate, sodium acid pyrophosphate and sodium bicarbonate. When water is added, carbon dioxide is released causing a gentle pressure in the rectum. Prelubrication with petroleum jelly is to be avoided since this may impair release of carbon dioxide.

### COMMENT

A review of the literature has confirmed Griener's original premise that laxatives as a group are sup-

ported by the weakest series of studies.<sup>13</sup> This is especially true for combination products since they are rarely tested against each individual ingredient. At present, use of these multi-drug products must be weighed against the possibility of inducing unexpected or unnecessary side effects.

Chronic laxative abuse is prevalent today due to the erroneous concept of the need for a daily bowel movement, advertising, and the ready availability of stimulant cathartics. Bowel retraining can be a very difficult and time consuming process. It is also frustrating that most patients prefer to return to the irritant laxative to which they have been addicted.<sup>31</sup>

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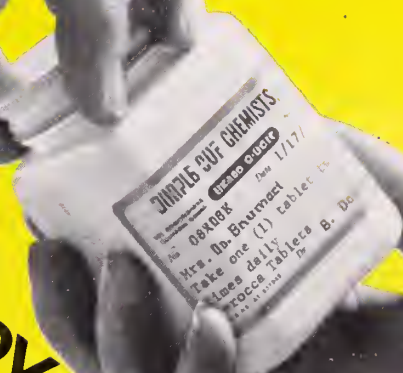
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## Maine Blue Cross and Blue Shield News

### FURTHER SCANNERS OPPOSED

At its November meeting, the Blue Cross and Blue Shield of Maine Board voted to oppose further CT (computed tomography) scanner applications until the health planning agencies have developed criteria for assessing need. The Board further voted that in the case of future CT scanner purchases made by physicians, whose equipment purchases are presently not reviewable by planning agencies or Blue Cross, Blue Shield payment will not be made for the equipment portion of the scanning charge (approximately \$175 to \$200) unless the purchaser receives approval of the Designated Planning Agency after review by the Maine Health Systems Agency. The professional component of the charge (about \$50) would still be paid.

Right now in Maine, there are three CT scanners either operational or on order, one at the Maine Medical Center in Portland, one at the Mid-Maine Medical Center in Waterville, and a physician owned-scanner in Bangor.

The technique is still considered experimental, especially body scanning, and there is no conclusive clinical evidence which demonstrates it improves the results of patient care.

Explaining the Blue Cross and Blue Shield position, Richard F. Nellson, President, said, "We have three scanners in Maine which cost about \$462,000 each with attendant annual operating costs of about \$180,000, or possibly higher. We felt it was time to stop and take a close look at how further scanner purchases would affect the cost and quality of Maine health care. We have taken action against further proliferation of CT scanners until assessment criteria are established in the knowledge that quality of care will not suffer. We feel that the three scanners provide strategic access from all areas of Maine and we can't afford not to put on the brakes at this point."

Blue Cross and Blue Shield of Maine will continue to oppose any CT scanner applications until data covering the use of the Portland, Waterville, and Bangor scanners has been accumulated and assessed by the health planning system for the purpose of establishing criteria for approval, at which time the company will reevaluate its position.

Since the financial resources available to the health care industry are not limitless, and until the questions of the productivity of CT scanning and the share of finances that should be devoted to this new technology and its ultimate growth and impact on health costs are researched, this policy will remain in effect. Blue Cross will work closely with health care providers, planning agencies and other organizations in the communities they serve as proper criteria for CT scanners are developed.



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## The "Other" Aspects of the Epilepsies

KARL E. SANZENBACHER, M.D.\*

The individual suffering from any of the epilepsies is faced with a myriad of problems. Only approximately half of their problems are medical. The purpose of this paper is to discuss the other problems which these patients face. Most of these problems are in social, educational, insurance, and employment fields.

One of the difficulties facing the patient is the lack of forceful advocacy. Because of the stigma attached to epilepsy, many of the problems which could be solved through legislation are not. Individual patients fear identifying themselves lest they place their relationship with their employer and neighbor into jeopardy. Fortunately, there has been a shift in public attitude towards epilepsy. Today, only 2% believe that epilepsy is a form of insanity and only 4% believe that epilepsy is caused by demonic possession, radioactive fall-out and other bizarre things.

The adult with epilepsy frequently feels that employment is the major problem. Yet, 80% of the patients whose epilepsy is well controlled are employed. However, 42% of adults in EFA studies noted difficulty in obtaining a job.

Fortunately, in the State of Maine an enlightened attitude persists regarding driving. Individuals with episodic loss of consciousness may apply to the Director of Public Safety for permission to drive. Such permission is usually based on a physician's report documenting the number of episodes that the patient has and the degree of control of these episodes. In this author's experience, if a patient has remained seizure free for a year, a license has been granted provided that the patient remains on medication. This situation is preferable to an across the board two or five year prohibition on driving without taking into consideration the individual aspects of the patient's case. For instance, the patient who

has an aura with his seizures usually would have ample time to pull a car over to the side of the road. In some patients who have just partial seizures without loss of consciousness may continue to operate a vehicle safely. It is this consideration of the individual aspects of each patient's case which indicates an enlightened attitude on the part of the Director of Public Safety and Maine law makers towards the Epilepsies.

Most persons with epilepsy can now purchase individual life insurance protection. The availability of insurance and the premium rate is dependent largely upon the type of epilepsy and other aspects of the patient's past medical history. For the patient with grand mal seizures, an increased premium is usually charged and this increase in premium rate varies with the year since the previous seizure. However, it may be as high as 250% if a grand mal seizure had occurred within two years. Many patients have difficulty obtaining coverage if the onset of their seizure was after the age of 40 or within a year of application.

For petit mal, coverage is more easily obtained but again it varies with the duration of the seizure free period and the frequency of seizures. Group life insurance is now available through the Epilepsy Foundation of America.

In the area of health insurance, the situation is more difficult. Fortunately, many patients can obtain group insurance. Some policies waive protection for disabilities or hospitalization due to seizure activity while others charge a higher premium. However, many patients with epilepsy find that this area of insurance coverage is the most difficult to them to obtain. It is of interest that the incidence of accidents among the epileptic population is no greater than the population as a whole.

In the area of education and training the problem is complex. School achievement may be affected by physiological, psychological and the social-envi-

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mental factors. Multiple *absence* seizures, many of which are frequently unobserved, may result in the child being thought of as retarded when in fact his intellectual capabilities may be normal. Other unobserved seizure phenomena with postictal confusion may result in similar changes in teacher attitude towards the child where the child is thought to be retarded or a behavior problem. Consequently, less is expected of him and the result is a lack in the normal progression in learning. One cannot overlook the side affects of medications, particularly when used in high doses. Other factors include parenteral overprotection and social rejection by classmates and teachers in restricting the progress of these students.

Emotional problems in children may be brought upon (1) by other children acting strangely towards the child, (2) by overprotection, (3) by changes in affect or emotional tone sometimes of a negative nature that are associated with some auras, and (4) by frequent medical visits which interfere with the student's attendance at school. Over solicitousness is almost as bad in its results as is rejection.

The learning of additional skills in vocational rehabilitation programs is a potentially beneficial factor in the individual's self-esteem and opportunities for obtaining employment. Frequently, the patient will be referred by the Department of Vocational Rehabilitation to a physician for an evaluation. This is to determine suitability for various rehabilitation programs. The report which the physician sends to the Vocational Rehabilitation Ser-

vice should describe the nature and number of seizures. The presence or absence of an aura is important in choosing work areas. Does the patient have complete loss of consciousness, partial loss of consciousness or no loss of consciousness? The level of anticonvulsants and their effects on the patient's coordination, level of consciousness and affect should be noted. Are there reflex or outside triggering phenomena which affect the incidence of seizures such as photic sensitivity?

Recently, the Maine Chapter of the Epilepsy Foundation of America became inactive. One of the predominate reasons despite its active programs of education was that there was a lack of support from the epileptic population themselves. In reviewing this with my patients, I have found that this was not due to an unwillingness to support the works of the group. In fact, the patient with epilepsy applauded and encouraged this work, but did so at a distance. Because of the threat of employability and the stigma which is still attached to the epilepsies, the individual patients were unwilling to come out and identify themselves as being epileptic. To support the group would possibly require such identification and therefore among the 20,000 patients with epilepsy in the State only a small number responded. It is only when the stigma has been removed through education of the public, employers, legislators and patients themselves will this vicious cycle finally end. Until that time, much of the total care — not just the medical aspects of care — falls to the medical profession.

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## Spring Meeting of the M.M.A. House of Delegates

Sunday, March 27, 1977

Eastern Maine Medical Center, Bangor, Maine

12:30 P.M. — Registration; 1:00 P.M. — Lunch; 2:00 P.M. — Meeting

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10:00 A.M. — Meeting of the Executive Committee

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For many years Robins has spotlighted the expectorant action of the Robitussin cough formulations by featuring action photographs of steam engines like the one on the preceding page. In keeping with this tradition, last year the company commissioned a well-known illustrator to render full-color drawings of several classic locomotives ... accurate to the minutest detail. Chances are you requested and received the first locomotive in this series, The William Mason, last winter. Now, the second one is available. (See below). To order your print suitable for framing, write "Robitussin Clear-Tract Engine #2" on your Rx pad and mail to "Vintage Locomotives," Dept. T4, A. H. Robins Company, 1407 Cummings Drive, Richmond, Va. 23220.



The Davis Camel (1873)

OUR PHOTO: Norfolk & Western Branch Train  
No. 202 west bound near Alvarado, Va (Oct., 1956).  
This line reaches the highest point of any railroad  
East of the Rockies (elevation 3,577 ft.) with a  
minimum grade of 3%. It crosses 108 bridges,  
some 700 ft. long! Photo by O. Winston Link.

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# Analysis of Experience With an Inpatient Alcoholism Treatment Program

PETER J. LEADLEY, M.D.,\* PAULA ROTH\*\* and DAVID MERK, M.A.†

## INTRODUCTION

The Kennebec Valley Comprehensive Alcohol Treatment Program is a combined venture operated jointly by both the Mid-Maine Medical Center and the Kennebec Valley Regional Health Agency. The Regional Health Agency is the recipient of a Title XX Grant from the State Department of Human Services to conduct an Alcoholism Treatment Program. The program began in February 1975, with the establishment of a 26-bed, inpatient, alcoholism rehabilitation unit located on the 6th floor of the Seton Unit of the Mid-Maine Medical Center. The Rehabilitation Unit, in which patients spend approximately 4 weeks and participate in the rehabilitation program consisting of lectures, group therapy, individual counseling, has been in operation slightly more than 1 and ½ years. During that period, over 400 patients have received alcoholism rehabilitation care. The Rehabilitation Unit is staffed by alcoholism counselors and associate counselors, registered nurses, and administrative personnel some of whom are employees of the Regional Health Agency and others of whom are employed by the Medical Center. There is a medical director, half-time, who is also a member of the medical staff. The relationship between the Medical Center and the Regional Health Agency in the operation of this program is defined by a contract which is negotiated yearly between the two agencies and specifies the responsibilities and authorities of each. The overall program director is an employee of the Regional Health Agency.

In January 1976, the program's Medical Director, who also serves as Medical Director for Alcoholism Treatment on the Medical Center's medical staff, initiated a detoxification program for patients who needed acute alcohol detox. care. With the assistance of the medical staff committee, a detoxification history, physical exam, routine orders protocol were formulated. Emergency Ward physicians from the Medical Center's fully staffed Emergency Ward were authorized to admit patients directly to a single patient floor using this standard protocol for management of alcoholism detoxification. The Department of Internal Medicine agreed to provide emergency coverage to this area for any problems that might develop after the patient was admitted.

The patient's subsequent management was assumed by the Medical Director for Alcoholism Treatment on the day following admission. A single medical ward was specified because of the need to provide additional training and experience for nursing staff in the management of alcoholism withdrawal and its complications. Although initial discussions centered around the concept of a "detox unit," there is no specific detox unit as such, and such patients may be admitted to any medical bed if space is not available on the designated ward.

The criteria used by the Emergency Department staff for admission of acutely intoxicated patients for detoxification are as follows:

- 1.) The presence of major alcohol withdrawal symptoms.
- 2.) The presence of other medical or surgical problems which themselves would not warrant admission which could be aggravated by alcohol withdrawal to a dangerous degree.
- 3.) The need for observation to rule out or observe for associated major medical or surgical problems which cannot be ruled out in the Emergency Ward.
- 4.) A total lack of other facilities or their unavailability which can afford competent, supervised detoxification and withdrawal management.

The data presented in this paper summarizes certain characteristics of the patients admitted to these two elements of the hospital based Alcoholism Treatment Program and also presents some information about patient outcome.

## METHOD

The data on patients admitted to detox. was collected from the charts of all patients admitted for detox. between January 1, 1976, when the detox. program was initiated and October 1, 1976, when the analysis was performed. Data was abstracted from the chart using appropriately trained clerical personnel.

The data on rehabilitation patients was collected as a part of another research effort designed primarily to quantify the use of ancillary hospital services by patients admitted for alcoholism rehabilitation. This latter work is awaiting publication.<sup>1</sup>

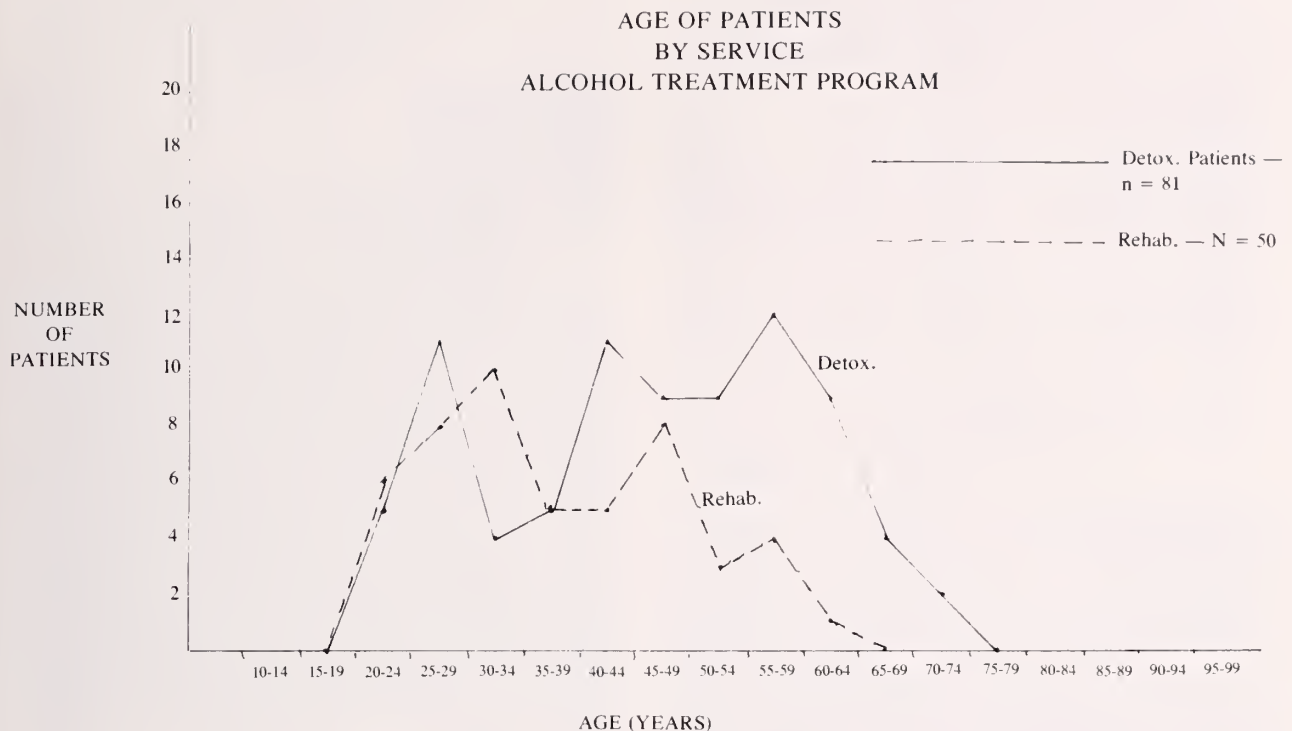
The data on the outcome of the rehabilitation process was collected by pooling all available information on patients who have been discharged from the program. This includes personal knowledge by members of the staff and other patients with whom contact has been maintained. Some patient survey questionnaires which have been mailed to

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Fig. 1



patients and returned and information gathered from the "grapevine;" Alcoholics Anonymous activities and the like was also included. In many cases several sources of information are used to cross check each other. The data presented are from the period of February 1975, when the program opened to March 31, 1976, and covers 340 different patients.

### RESULTS

**Detoxification Program:** During the period from January 1, 1976 to October 1, 1976, 103 admissions were recorded using the detox. protocol as described above. This period spanned 280 days of operation and the 103 admissions were recorded for 81 patients.

Of those patients admitted to the Detoxification Service, 42, or 51.9% came from the Medical Center's primary service area consisting of those communities immediately adjacent to Waterville in northern Kennebec County and several communities in southern Somerset County. Another 16 patients (19.8%) came from southern Kennebec County and 18 patients (22.2%) came from the remainder of the Medical Center's secondary service area. Five patients (6.2%) came from areas far removed from the hospital secondary service area and included several out of state patients. Thus, approximately one-half of the admissions to the detox. program consist of patients from the Medical Center's primary area and another half of patients from outside the immediate service area. The Medical Staff has extended a request to other hospitals within the Medical Center's secondary service area

to provide detoxification services for patients in their own communities.

The mean age of patients admitted for detoxification is 46.3 years with an age range of between 20 and 74 years. It is interesting that this mean age is approximately 9 years greater than the mean age of patients admitted for alcoholism rehabilitation (37.5 years). The age curves for both groups of patients (alcohol detox. and alcohol rehab.) are presented below in Figure 1. This figure also illustrates the somewhat greater age of patients admitted for alcoholism detoxification and also shows a biphasic curve for alcoholism detoxification similar to that observed for patients admitted to the medical and surgical services of the Medical Center.<sup>1</sup>

Of the 81 patients treated in the detox. program, 13 patients (16.1%) were repeaters during this 9 month period. The number of repeat admissions for this recidivistic group ranged between 1 and 5, and this group of 13 patients had a mean detox. admission rate of 2.7 admissions per patient.

The detoxification patients were 82.7% male and this corresponds almost exactly with the sex distribution of patients in the Rehabilitation Unit, which were found to be 78.0% male.<sup>1</sup>

The 103 detox. admissions were analyzed for length of stay. This group of patients generated 328 patient days of hospital care during the nine month period for a mean hospital stay of 3.18 days. The range of stay was from 0 to 21 days (some patients left on the same day they arrived and thus generated a hospital stay of 0 days). This experience is quite similar to the Professional Activity Study data

TABLE 1

DISPOSITION OF ALCOHOL DETOX. PATIENTS			
Age Group	All Ages	Less than 48	48 and Older
Transferred to Rehab. and Completed	18.5%	17.0%	19.6%
Transferred to Rehab. and then left AMA	14.6%	17.0%	12.5%
Left Detox. AMA	27.2%	34.0%	26.8%
Discharged from Detox.	36.9%	29.8%	37.5%
Transferred to Another Facility	2.9%	2.1%	3.6%
TOTAL	100.0%		
Transferred to Rehab.	33.1%	34.0%	32.1%
Left AMA	41.8%	51.0%	39.3%

TABLE 2

INSURANCE COVERAGE		
	Patients in Detox.	Patients in Rehab.
% with Health Insurance	50.6%	50.0%
% of Insured with:		
Blue Cross	29.3%	32.0%
Medicaid (XIX)	31.7%	40.0%
Medicare (XVIII)	31.7%	4.0%

which has been used for utilization review. There was only a small number of patients whose length of stay was greater than 7 days and these were invariably patients who experienced severe complications of alcohol withdrawal.

Analysis of the same data shows that the average census of patients admitted for detoxification was 1.14 patients per day, and a range of the census was between 0 and 7 patients on any given day.

A great deal of interest has been repeatedly expressed in what happens to the patients admitted for detoxification. Data on these 103 admissions is presented in Table 1. Of all detox. admissions, 18.5% were transferred to the Rehabilitation Unit and completed the Rehabilitation Program. Another 14.6% were transferred to the Rehabilitation Unit and subsequently left the Unit against medical advice. Twenty-seven and two-tenths percent of the admissions were terminated by the patient leaving the detox. program against medical advice; 36.9% of the admissions were terminated by the patients being discharged from the detox. program; and 2.9% of the admissions ended by the patient being transferred to another alcoholism treatment facility. In total, 33.1% or approximately  $\frac{1}{3}$  of the patients were transferred to the Rehabilitation Unit and in turn approximately  $\frac{1}{2}$  of these subsequently signed out against medical advice, leaving  $\frac{1}{2}$  or approximately  $\frac{1}{6}$  the total to successfully complete the program. Also, of the total 103 admissions for detoxification, 41.8% of the patients ultimately signed out of the hospital against medical advice, either directly from the detoxification program or from the Rehabilitation Unit, where they had been transferred.

Table 1 also displays similar information for that group of alcohol detoxification patients less than 48 years of age (the median figure) and for that group of

TABLE 3

ALCOHOL RELATED — COMPLICATIONS PATIENTS IN DETOX. (103 admissions)	
Abstinence Syndrome	100%
Withdrawal Seizures	5.8%
Delirium Tremens	2.9%
Alcoholic Hallucinosi	1.0%
Alcoholic Liver Disease	4.9%
Others: Associated overdose — one patient	
Alcoholic cardiomyopathy — one patient	
Chronic pancreatitis — two patients	

alcohol detoxification patients 48 years of age and older. Examination of this data shows that similar proportions of both age groups were transferred to the Rehabilitation Program and completed the program. The younger patient group, however, had a greater tendency to sign out of both the detox. program and the Rehabilitation Unit against medical advice. However, the older patient group had a much greater tendency to be discharged directly from the detoxification program without being transferred to the Rehabilitation Unit. It may be that this tendency (which was not suspected before the analysis) reflects the greater refractoriness of older and more established alcoholic patients to rehabilitation attempts.

Table 2 below shows the distribution of the health insurance coverage for both the patients in the detoxification program and the patients in the Rehabilitation Program. For the detox. patients, 50.6% had health insurance as compared with 50.0% for the rehabilitation patients. Differences exist between the two groups, however, in terms of the kind of insurance which was possessed. A higher proportion of detoxification patients had health insurance through the Medicare (Title 18) Program and this difference is consistent with their relatively greater age.

Table 3 displays the alcohol related complications that were seen among these 103 admissions to the alcohol detoxification program. All of the patients admitted exhibited the alcohol abstinence or withdrawal syndrome to varying degrees. This syndrome consisted of tremor, anxiety, nausea and vomiting, anorexia, diaphoresis, and insomnia. Tachycardia, hypertension, elevated blood sugar, elevated blood uric acid, elevated SGOT, and macrocytosis with mean corpuscular volume of greater than 92 cubic micra were also commonly observed. Five and eight-tenths percent of the patients exhibited alcohol withdrawal seizures, 2.9% exhibited true, full-blown delirium tremens, 1.0% exhibited alcoholic hallucinosis and 4.9% exhibited evidence of alcoholic liver disease as manifest by enzyme changes and elevated serum bilirubin. Additional complications observed were an associated drug overdose in one patient, alcohol cardiomyopathy with congestive heart failure in one patient, and two patients who had recurrence of well-documented chronic pancreatitis during their detoxification admission. It should be noted at this point that the

prevalence of alcoholic liver disease is probably markedly underestimated in this group. This is because the routine detoxification orders do not require that all patients be tested with serum enzymes and bilirubin for this problem. These tests are ordered only if there is a specific indication.

**Rehabilitation Unit Patients:** Data on the Rehabilitation Unit patients was obtained from a random sample of 50 patient charts from patients admitted to the Rehabilitation Unit during the calendar year 1975. The sample was drawn according to standard random sampling techniques. Some information derived from this sample, such as information on the mean patient age, insurance coverage, and sex distribution has already been presented. As was mentioned above, the average age of patients on the Rehabilitation Unit was approximately 9 years less than that of patients in detoxification program and was approximately 37.5 years. The Rehabilitation Program is structured in such a way that the average patient can complete the program in approximately 4 weeks. However, other data has shown that only 87% of admitted patients complete this Rehabilitation Program; the remaining 13% sign out against medical advice. Accordingly, the mean length of stay for patients admitted to the Alcoholism Rehabilitation Unit is 23.3 days.<sup>1</sup> Other data reported elsewhere has also documented that in addition to staying in the hospital much longer, alcoholism rehabilitation patients have a significantly lower daily utilization of laboratory tests, x-ray studies, electrodiagnostic studies, and specialty consultations than do patients on the medical and surgical services of this same Medical Center.

As was mentioned above, 50.0% of the alcoholism rehabilitation patients possess health insurance which provides partial or total coverage for their treatment. Only a very small number of alcoholism rehabilitation patients derive such coverage through the Medicare or Title 18 Program (see Table 2).

**Follow-up Information On The Alcoholism Rehabilitation Unit:** The following data was derived in the manner described above from a group of 264 patients who had completed the Alcoholism Rehabilitation Unit Program between February 1975, and March 31, 1976. Of this group of 264, 117 (45%) had been continuously sober since their discharge from the program. Another 64 patients were sober at the time the data was collected, but had had some "slips." This group, which consisted of 24% of the total, however, had significantly altered their pre-treatment drinking pattern. Sixty-two members of this group (23%) were actively drinking at the time of this study, and 4 patients (1.5%) were deceased. The follow-up period varied in length from two weeks to 13 months. Obviously, the chance of re-summing drinking is greater the longer the time since discharge, and accordingly, the data was analyzed for four patient groups broken down into different intervals after discharge. This data is displayed in Table 4 and shows that, as would be expected, the

TABLE 4

BREAKDOWN OF STATISTICS FOR PEOPLE WHO COMPLETED THE PROGRAM (By Length of Time Since Discharge)				
	Out at least 9 months	Out 6 to 9 months	Out 3 to 6 months	Out less than 3 months
Sober Continuously	32 (38%)	25 (41%)	31 (46%)	29 (54%)
Sober now after a few slips	21 (25%)	15 (25%)	20 (30%)	8 (15%)
Actively drinking	23 (28%)	16 (27%)	16 (24%)	7 (13%)
Unknown	3 (4%)	4 (7%)	0 (0%)	10 (18%)
Deceased	4 (5%)	0 (0%)	0 (0%)	0 (0%)
TOTALS	83	60	67	54

proportion of those remaining continuously sober declines from 54% of the group that has been out less than three months to 38% of that group which has been out at least 9 months. Likewise, the proportion of patients actively drinking increased from 13% to 28% over the same groups. Data is also presented on that group of patients whose drinking habits were totally unknown at the time of the study. As was mentioned above, the information was gathered from all available sources.

Of the 264 people completing the program as of March 31, 1976, 129 (49%) were known to be actively working at the time of the study. Thirty-one (12%) were retired or disabled at the time of the study.

From data presented earlier, it was shown that 18.5% of patients admitted for detoxification were subsequently transferred to the Rehabilitation Program and also completed this program. Using a figure of 40% as the expected proportion of patients who maintain continuous sobriety over a 9 month period after rehabilitation treatment, it can be seen that of the total of 81 patients admitted for detoxification during the 9 month study period, 8 such patients can be expected to remain sober for a period of 9 months as a result of their treatment. Thus, the yield of the detoxification program in terms of patients continuously sober 9 months is 9.8%. This figure, obviously, does not represent the yield of the Alcoholism Rehabilitation Program since the majority of patients admitted to that program are not admitted from the detoxification program at this Medical Center but are transferred from other treatment programs or are admitted directly after alcohol withdrawal has been completed at home or elsewhere.

## DISCUSSION

These data are presented to describe the operation of the inpatient Alcoholism Treatment Program within a community Medical Center in the State of Maine. It should be emphasized in reporting and

interpreting them that the treatment program is still relatively young and hopefully through continued analysis of information such as this and subsequent revision of the treatment process, improvement in these results will be manifest. They are also presented because they may prove useful to other institutions and planning agencies who are considering the development of other alcoholism treatment programs in areas with similar geographic, social, and economic characteristics.

The utilization of the detoxification service as described above was approximately similar to that which had been predicted while the service was in the planning stage. The program has showed evidence of slight growth both in terms of patient census and number of admissions since it was begun approximately 10 months ago. We note with interest the fact that patients in the detoxification program tend to be older than their counterparts in the Rehabilitation Unit. As was mentioned above, this may be related to the fact that older patients who have progressed further in their alcoholism are generally regarded as being less responsive to rehabilitation treatment. It is also possible that the greater age of the detoxification patients reflects the additional amount of time necessary for their alcoholism to progress to the point where they need medical management for their withdrawal symptoms. It has been our general experience that the withdrawal symptoms among the younger patients have been much less profound; and to be sure many of these younger patients have completed alcohol withdrawal at home before being admitted for alcohol rehabilitation.

The information presented above also shows that a fairly large proportion of alcohol patients sign out of the program prematurely. This proportion is clearly much larger for patients admitted to the detoxification program (42%) as opposed to all patients admitted to the Rehabilitation Unit without previous inpatient detoxification (13%). Again, this greater percentage may reflect the degree to which patients who need admission for detoxification have more severe illness and one of the manifestations of this severity is their unwillingness or inability to complete a structured treatment process. This tendency to sign out against medical advice is much more pronounced for the younger patients (51.0%) as opposed to the older patients (39.3%).

The data presented in Table 2 shows that approximately half of both patient groups have health insurance which pays for part or all of their inpatient care. For those patients admitted to the Alcoholism Rehabilitation Unit who did not have health insurance, the Title XX Grant was designed to support their care in those situations where they could not afford to pay for their own care. However, the patients in the detoxification program who did not have appropriate health insurance and who could not afford to pay for their own care are supported through the Medical Center's charity or free care

policy. It would appear that more liberal health insurance to cover this need would be helpful.

The incidence of alcohol withdrawal complications was approximately that which has been reported a number of times in the literature.<sup>2</sup> As was mentioned above, the prevalence of alcohol liver disease in this group is probably markedly under-reported in this sample because routine liver tests were not always done. Liver tests were ordered only when specific indications existed for their use. In total, 3 patients experienced true delirium tremens. Only two of these patients had what might be called "full-blown" delirium tremens, and the other patient was transiently delirious for approximately one day.

The male sex preponderance is consistent with the experience reported from a number of other alcoholism treatment centers.<sup>3</sup> A great deal of interest has recently been generated in women alcoholics and the Director of this program is currently formulating plans for a more aggressive and active approach to women with drinking problems. Most authorities feel that there are as many women alcoholics in our society as men but for a variety of social reasons the prevalence of alcoholism among women is markedly under-reported.

The data on the Rehabilitation Unit is also presented primarily for descriptive purposes. The relatively low utilization of ancillary services by this group reported elsewhere may have significant implications for hospital planning and other similar activities.<sup>1</sup>

The outcome data from the Rehabilitation Unit is clearly of great interest. Again, it should be stressed that these figures come from the first 15 months of the program's operation, and it would be reasonable to expect that increasing familiarity of the staff with the treatment process and the greater skill that comes with experience should produce better results in the future. All in all, the results suggested approximately 70% of the patients who have completed the Rehabilitation Program significantly change their drinking pattern after discharge. The majority have remained continuously sober, and another significant group continues to have "slips" but in general maintains a drinking pattern that is different from the pre-treatment pattern. We fully expect that as time goes by a significant portion of that group who is now experiencing slips will be re-treated, and hopefully such re-treatment will increase the proportion of program participants who are able to maintain continuous sobriety.

Despite the usual pitfalls and problems associated with the development and operation of a new program, the alcoholism treatment activities at Mid-Maine Medical Center have proceeded remarkably smoothly. Since the program's inception in early 1975, well over 500 patients have been treated in one way or another. Of this group only one fatality occurred. This occurred in a 45-year-old woman who died in the Intensive Care Unit of fulminant hepatic

insufficiency and hepatorenal syndrome developing as a result of severe alcoholic hepatitis. This patient had never received rehabilitation care.

The detoxification and Rehabilitation Programs outlined above constitute the first two elements in the total treatment process which is conducted by the Kennebec Valley Comprehensive Alcoholism Treatment Program. The third element consists of a 23 month outpatient group therapy program. This commences at the time of discharge from the Rehabilitation Unit and continues so that the patient receives a period of treatment of 2 years' duration total. This program is actively in operation at the present time but, obviously, has not yet graduated its first group of clients. These are scheduled to graduate in the spring of 1977. We hope that in subsequent future reports we shall be able to report more fully on the outcome of patients who have completed the entire 24 month treatment process. We interpret these preliminary and initial results as being very heartening and to suggest that alcoholism treatment has a significant and important place in the spectrum of services offered by a community Medical Center and a community based Regional Health Agency.

#### SUMMARY

Data are presented on the first one and one-half year's operation of a comprehensive alcohol treatment program operated jointly by the Kennebec Valley Regional Health Agency and the Mid-Maine Medical Center. The detoxification phase of the treatment process has been in operation approximately 10 months; has treated slightly over 80 patients, and approximately 1/3 of the patients entering the detox. phase are transferred to the inpatient rehabilitation phase of the program. The incidence of severe complications of alcohol withdrawal in the

detoxification phase is low and consistent with that reported in the literature. Approximately 40% of the patients admitted to the detoxification phase sign out against medical advice at some point after admission.

The inpatient rehabilitation program averages 4 weeks in duration and experiences a 10 to 15% sign-out rate. Patients in the Rehabilitation Unit are slightly younger than those in the detox. program by approximately 9 years. Almost exactly one-half the patients in both elements of the program have their care paid for by third-party carriers.

The follow-up results of the inpatient rehabilitation unit suggest that approximately 70% of the patients who complete the inpatient rehabilitation program manifest a significant alteration from their pre-treatment drinking patterns. The proportion of discharged patients who maintained continuous sobriety gradually decreases with time, such that 38% of the discharged patients remain continuously sober for a period of nine months. The follow-up results also suggest that approximately 10% of the patients who enter the detoxification element of the program will continue to be continuously sober for 9 months after their discharge from inpatient rehabilitation. The experience in the operation of this treatment program clearly suggests that inpatient alcoholism treatment is an important part of the services which can be offered to the community by a community Medical Center in conjunction with a vigorous, community based Home Health Agency.

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## *Annual Meeting Dates For Your 1977 Calendar . . .*

Maine Medical Association, June 11-14  
Treadway-Samoset, Rockport, Maine

American Medical Association, June 18-23  
San Francisco

# Statistical Summary of the Activity of the Laser Department, Ophthalmological Service, Mid-Maine Medical Center

RICHARD H. DENNIS, M.D.\*

The purpose of this paper is simply to provide a statistical indication of the activity of our Laser Department. The period covered is approximately two-and-a-half years from March of 1974 to September of 1976.

The total number of patients seen and the total number of visits made are summarized. The number of treatments by the Laser are given and the photographic surveys are recorded. It must be remembered that more than one photographic survey and more than one treatment may be given on the same patient. On the other hand, many patients are photographed and not treated. The services of this Department are being more and more utilized by other departments and services in the Hospital for photographic and recording purposes. In these patients, of course, no treatment is contemplated and the patient is considered as a unit for photographic survey only.

No attempt is made to indicate success or lack of success of treatment nor of improvement or retrogression of conditions during the course of treatment. Diabetic patients, as everyone knows, vary a great deal. They are, by far, the greatest percentage of patients seen and especially treated. Their course is stormy and fraught with recurrent hemorrhages, proliferating tissue, and loss of vision. The aim of Laser treatment is to minimize this. No indication is ever given to the patient that the Laser is the Answer to Diabetic Retinopathy. I am sure they are all well aware of this before they have their first treatment in our Laser Department. The results of Laser treatment in Diabetes can only be assayed on a very large statistical basis. This has, of course, been done in the "Collaborative Study." The latter is a large continuing study, carried out in a dozen Laser Centers located in University-type settings doing a large number of patients. Thus, their combined results carry a statistical significance. (A.J.O. April '76). From the latter, it has been tentatively decided that probably the only treatment which can be considered beneficial on a statistical basis is peripheral ablation in regard to neovascularization and minimizing of hemorrhages. It would seem, in our small service, that the patients who have had peripheral ablation do seem to have a "dry retina" and appear to be arrested for at least the short period

of time encompassed by the life of our Laser Department.

As far as the application of the Laser to retinal holes, tears, and postoperative supplementation of surgical detachment cases, we feel that they have been highly successful. We have not had one, so far, which has not responded to this type of treatment, including the detachments which have had "touch-up" Laser treatment following a surgical buckling.

In regard to the statistical results of any other treatment which we have carried out, the limited number of cases precludes drawing any conclusions.

The Laser Department is set up in the Thayer Unit of Mid-Maine Medical Center. It was initiated by a federal grant of moderate amount. This has been supplemented by the Hospital itself to a much larger degree. We now have four rooms, including a waiting room, photographic room, examining and Laser treatment room, and a commodious dark room. The facilities of the Unit are being utilized more and more, not only by patients from surrounding areas, but also by the other departments and services in the Hospital itself. We find that the photographic service and the dark room are much used by the Education Department in preparation of lectures and their slides. It is also used by the Public Relations Department in its promotion of literature and releases. It is utilized by other Doctors on the Staff in preparing papers and lectures and in their discussions. Up until now, we have had enough time available so that these services, in addition to the directly related Laser activities, can be carried out without interfering with the prime function of the Unit. The Laser Department was and has been very happy to be able to provide these ancillary services.

The operation of the Laser Department has become organized and simple. Although we do have complete examining equipment in the Laser Lab, we find in the Eye Service, that it is more efficient and also effective for us to have the patients report to our office first. Here they are given a complete examination and this can be done much more easily in the office environment than in the Laser Lab at the present time.

Following their examination in the office, during which time they are dilated, they are immediately sent over to the Laser Lab.

At the Lab, they are photographed with Polaroid film for our own records and for returning to the re-

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ferring doctor if the case warrants it. They are then photographed in Kodachrome® and finally are photographed after the injection of fluorescein.

If it is obvious that treatment will have to be carried out and this can be ascertained even before the Fluorescein pictures are read, the patients are then treated that afternoon. If further treatment is contemplated, it can almost always be done on an out-patient basis. Occasional cases of severe diabetics have been kept in the Hospital overnight or for two nights in order to complete the series of Laser treatments to be given at that time.

If, for various reasons, treatment is not contemplated for that day, a written report is sent to the patient within a week. Along with this is an accompanying appointment for Laser treatment if the latter is indicated. Many times these patients are not prepared to stay longer than their first visit as they have other commitments elsewhere. When their appointment is made for the Laser treatment, it is indicated as to whether it will be out-patient or whether it will require an in-patient stay. The latter is sometimes used for patients who are particularly apprehensive, or who we have decided, during the first visit, probably will need some sedation in order to be able to withstand the Laser treatment itself. In the past, we have had several patients who have felt so much pain and discomfort that they could not complete the treatment on an out-patient basis. These patients have been admitted, given some systemic medication, and have in all cases, been able to complete the series of treatments. Only one of our patients has required any anesthesia and this was in the form of a retro-bulbar injection.

If the patient is to stay two or three days for his treatment, and if his condition warrants this, he is admitted. Otherwise, they make their own arrangements and as of now, the patients do not seem to have had any difficulty in finding accommodations for this purpose.

A summary of the patients follows. One must remember that the total number of individuals as of the closing of the records for this report was 547. The number of patients seen each year far exceeds this. This is obviously because many of these patients are repeated.

As one can see, the total number of visits has steadily increased throughout the life of the Laser Lab and most markedly in this last year of 1976. It is of interest that there are a large number of photographic surveys carried out in contrast to the number of Laser treatments. No summary of photo-

graphic activity other than that directly related to the Laser Laboratory activity itself has been included.

We have next classified the patients by Diagnosis and have summarized only those which appear to be most important and most interesting. Not all of the cases are listed in the following summary. The Diseases have been listed numerically according to the frequency of the diagnosis. The number of patients treated for each diagnosis is indicated. We have been conservative in using the Laser. As we become more and more adept at diagnosing the Fluorescein Angiography and the Kodachrome Photography, we will be doing more treatments. Our aim at the present time is to attempt to help but to try not to harm anyone. As far as we can determine up until now, we have avoided the latter.

#### CLASSIFICATION OF PATIENTS BY DIAGNOSIS

	<i>Seen</i>	<i>Treated</i>
1. Diabetic Retinopathy	201	96
2. Macular Degeneration	50	2
3. Retinal Detachments	41	32
4. Central Retinal Vein Occlusion	21	4
5. Central Angiospastic Retinopathy	10	2
6. Central Serous Retinopathy	17	7
7. Papilledema	16	0
8. R.P.E. Detachments	12	5
9. Macular Edema	10	2
10. Macular Hemorrhage	9	0
11. Pigmented Lesion or Nevus	9	0
12. Retinal Hemorrhage	9	0
13. Disciform Degeneration	8	1
14. Branch Vein Occlusion	7	0
15. Toxoplasmosis	5	0
16. Macular Cyst	5	0
17. Tumors	3	0
18. Histoplasmosis	3	1
19. Central Artery Occlusion	3	0
20. Macular Hole	3	0
21. Doynes Degeneration	2	0
22. Optic Neuritis	2	0
23. Iris Tumor	2	0
24. Toxicara Canis	1	0
25. Synechiectomy	1	1
26. Vascular Maculopathy of undetermined etiology with hemorrhage and leakage	27	1

In summary, a simple statistical summary of the activity of the Laser Department of the Mid-Maine Medical Center has been presented. No attempt has been made to judge the efficacy of the Laser treatment. Our feeling is similar to that of the Collaborative Study. It appears that the Peripheral Ablation does help some people.

In regard to retinal detachment cases, we feel very definitely and know with a direct certainty, that the Laser has been a great help as an adjunct to our treatment in these cases.

Beyond this, we are not in a position to assess the value of the Laser as of the present time.

We plan to evaluate our patients in another two years, at which time we will have enough data in various categories to make some statistically valid assessments.

	<i>March Dec. 1974</i>	<i>Jan. Dec. 1975</i>	<i>Jan. Sept. 1976</i>
TOTAL # PATIENTS	188	325	402
TOTAL # VISITS	204	329	441
TOTAL # PHOTOGRAPHIC SURVEYS	221	253	365
TOTAL # LASER TREATMENTS	71	120	182

# Eosinophilic Granuloma of Bone

ROBERT I. ROY, M.D.\*

Although the etiology of eosinophilic granuloma remains unknown, increasing clinical experience and increasing amounts of histopathological data have brought about significant conceptual changes in the classification of Hand-Schüller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma of bone. There is a distinct trend away from the "lumping" of these various clinical entities as various manifestations of histiocytosis X. Lichtenstein first suggested this all inclusive nosological term in 1953.<sup>1</sup> The tendency to group these clinical entities together based on their microscopic histopathology is understandable, but the distinctly different patterns of biologic behavior and prognosis justifies their clinical separation. The critical reappraisal of histiocytosis X complex was solidly challenged by Lieberman et al in 1964, when they published their extensive review of a large number of cases in which they could personally review the histopathological material and the case records with clinical follow-up of over 80 cases.<sup>2</sup> Their study clearly demonstrates that eosinophilic granuloma of bone has a clinical course and prognosis very distinct from the other reticuloendotheliosis.

Despite its unknown etiology, the gross and microscopic anatomy of eosinophilic granuloma of bone is well recognized. It presents as an osteolytic, granulomatous lesion in bone. Microscopically, the lesion is made up of histocytes and eosinophiles with an occasional multinucleated giant cell. It can occur in an unifocal (monostotic) or multifocal (polyostotic) form. In the flat bones, such as the skull, the pelvis, or the scapula, the radiologic picture is of a "punched out" lytic lesion with no radiographically obvious reactive bone at the tumor-host interface. In the long bones, the lytic lesion is centrally located and the reactive bone at the periphery of the lesion is seen radiographically as periosteal new bone formation which helps to separate it radiographically from the unicameral bone cyst. The simple bone cyst does not elicit periosteal new bone formation unless a pathological fracture has occurred. When an eosinophilic granuloma of bone arises on the diaphyseal portion of a long bone, the associated periosteal new bone formation can create a radiographic picture of Ewing's sarcoma that is resolved only by histopathological examination. The other radiographic lesion that bears some similarity to eosinophilic granuloma is fibrous dysplasia. The distinguishing radiographic feature with fibrous dysplasia is the "ground glass" appearance of the lesion. This characteristic is due to the uni-

formly distributed immature trabeculae of bone within the lesion which gives it a radiographic density greater than the nearby soft tissues but less than normal bone.

Some of the statistical data is of clinical importance when the physician encounters the skeletal lesion of eosinophilic granuloma. About 20% of the monostotic lesions seen in childhood will in time develop into the polyostotic form with or without systemic involvement.<sup>3</sup> About 50% of the monostotic cases occur in patients over 10 years old with the skull, pelvis, vertebra, ribs, and proximal ends of the long bones being the most common sites of occurrence. When you consider patients over 15 years of age, the ribs are the most prevalent site of the lesion. Often times the complaint of pain after minor trauma or simply heavy manual labor leads to an x-ray and to the diagnosis of a pathological fracture in a lytic rib lesion. Tomography is helpful in both seeing the cortical break of the pathological fracture or the stippled calcification of a cartilagenous lesion (enchondroma).

When the vertebral body of a child is involved, eosinophilic granuloma of bone presents as a flattening of the vertebral body (vertebra plana or Clave's disease) with increased radiodensity secondary to the compression fracture of the mechanically weakened vertebra. In certain critical areas of the spine, stability is compromised and cord compression can occur.

Adequate evaluation should include a CBC with sedimentation rate, alkaline phosphatase, serum calcium, and phosphorus determination, chest x-ray and skeletal survey. The Tc<sup>99</sup> polyphosphate bone scan is most helpful in detecting occult lesions which escape the routine skeletal survey. Likewise tomography, as previously noted, is useful in detecting the lesion's occult pathologic fracture or the stippled calcifications of a cartilagenous lesion.

Once the patient's evaluation is complete, surgical biopsy is very often indicated. If the lesion is in critical weight bearing area where pathological fracture has occurred or may occur, then curettage and packing with autogenous bonegraft is indicated. If the lesion is very large necessitating a great deal of autogenous bone graft, the surgeon could consider the use of sterile, freezer-dried cortical bone chips from the U. S. Navy Bone Bank at Bethesda, Maryland as a useful alternative to "harvesting" half of the child's ilium. Radiation therapy is no longer indicated as a therapeutic modality except in the occasional case of vertebral involvement where stability is being compromised and the spinal cord is at risk. In these circumstances low dose radiotherapy in the range of 600-1000 r has been accom-

*Continued on Page 57*

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# Small Area Variations in Health Care Delivery

## A Critique

FRANCIS D. MOORE, M.D.\*

Two recent articles by Wennberg and Gittelsohn<sup>1,2</sup> demonstrate seemingly remarkable variations between small local areas, in the extent to which surgical operations and certain other health services are utilized. The two articles deal respectively with the states of Vermont and Maine.

While it is essential that students of medical care and socio-economics examine health services in relation to populations served, restraint must be exercised in evaluating results when they pertain to small areas, small populations, and infrequent episodes. There is something about the data and conclusion in both these articles that does not ring true with experience or intuition. The variations do not appear important in terms of ordinary medical care distribution kinetics. The two articles therefore mandate a critique. It is the purpose of this brief commentary to raise some of those nagging questions about the authors' conclusions and the statistical handling of variations in infrequent events (i.e. surgical procedures) in very small populations, as well as selection of procedures for study.

First off, let us quote the major thesis and conclusion of these two workers, drawn from both of these studies. Their view as set forth in the Maine study is as follows:

"While each factor undoubtedly contributes in some degree to patterns of health care consumption, the thrust of the evidence is that supply factors are more important than consumer behavior in determining the relative rate of use of surgical care among neighboring geographic areas."

Stated otherwise, the authors contend that "provider factors" such as the capricious whim of hospitals, physicians, and surgeons determine these allegedly remarkable variations.

Let us start our commentary by asking three important questions which we will return to at the end.

1) Why did these authors fail to examine two very common surgical procedures, namely, *obstetrical delivery* and the *reduction of fractures*, in which the capricious whim of hospitals, surgeons or physicians has absolutely nothing whatsoever to do with local incidence? These two categories of medical episode are independent of provider behavior, and unaffected by personal or fiscal motivation of physi-

cians or surgeons. Or, is it possible that the authors did examine these two categories, and, discovering that the data failed to support their thesis, then omit them from the published report?

2) Considering the fact that some of the procedures examined are rare statistical events, affecting less than one person per 1,000 population per year, why did the authors fail to examine *variations between years*? Would it not be entirely possible that variations between successive years might be just as great as the variations between local geographical areas? If so, the postulate as well as the conclusions of the authors, simply vanish.

3) Why did the authors omit any sort of *control information*? Why did the authors fail to publish some control data, to make a meaningful comparison with other socio-economic variables? Such might be housing starts, sales of refrigerators, or television sets, or percent of registered voters voting. Admissions to mental hospitals also provide a useful control. These data would have provided some concept of the normal biological and demographic variability of small population behavior patterns in two rural states of New England. Demand factors are important in some of these variables and not in others.

Because of recent experience in studying small variations in surgical care in Maine and Massachusetts,<sup>3</sup> and participation in the National Surgical Study (SOSSUS)<sup>4</sup> the author is qualified to comment on the surgical data of these authors. There are other problems in these articles, of a statistical and demographic nature, that others are better equipped to criticize.

In the studies of Vermont and Maine the authors have concentrated on the data for nine surgical operations as carried out in a single year; tonsillectomy, appendectomy, hemorrhoidectomy, herniorrhaphy, prostatectomy, cholectectomy, hysterectomy, dilatation and curettage, and varicose veins.

With the exception of appendectomy for acute appendicitis, all of these procedures are operations for which the indications for surgery depend upon a very important personal interaction between the patient, the referring physician, and the surgeon. These operations are of a discretionary type. The demand factors are traceable to the patients' symptomatic perceptions, and the willingness of the internist or family physician to "put up with" the complaints, or treat them symptomatically, rather

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than referring to a surgeon. The most important question is "how much is it bothering you?" It is of course understandable that different levels of sophistication or economic resource will bring patients to the surgeon for hernia repair according to the degree of tolerance the patient has for the minor discomfort of a hernia. To assume that alterations in herniorrhaphy repair are always related to "provider factors" is a gross oversimplification. And yet it seems self-evident that the patient will more likely seek repair of a simple mildly symptomatic hernia, when there is a surgeon of his acquaintance to whom he can turn in his own local district. One of the platitudes of medical sociology holds that "no psychiatrist, no psychoanalysis, no surgeon, no surgery."

The authors have then presented figures for the total number of surgical operations for each state and for the incidence of these procedures in various arbitrarily designated health delivery areas. The latter are incomplete. In the case of Vermont, they do not include in their study the health service areas that border on New Hampshire. In the state of Maine they completely omit large northern and central areas, presumably because they are thinly populated. In so doing they have, seemingly carelessly, completely omitted mention and presumably study of more than 20 hospitals in Maine — almost one-half the total number of hospitals (46) in the state! Incomplete data for states or regions can be misleading. The article by Lewis, quoted by these authors for similar variations in Kansas<sup>5</sup> is a notable example of this phenomena since Lewis confined himself to some insurance programs that only included about 35% of the population of the state and he omitted patients from the eastern end of Kansas going to the Mayo Clinic and the western end going to Denver, unless they had the particular sort of insurance that formed the basis of case selection.

The total number of operations carried out for Vermont, as based on the data of these two authors, shows a variation of 36-69 operations per 1,000 population per year, with a statewide average of 55. The data for the four areas studied by SOSSUS (two of which were in New England) showed a variation of 58-91 operations per 1,000 population. Wennberg's data on Maine do not show total operations but are based on "surgical discharges" (a slightly different but nonetheless comparable statistic) showing a range from 58-95 operations per 1,000 per year. As a generality, variations among small units will be greater than variations among larger statistical units. The populations in the SOSSUS study areas range around 1,000,000; the areas in Vermont and Maine are much smaller, ranging from areas including as few as 8,000 population to areas as large as 171,000. It is hardly surprising that variations among small areas will be greater than they were in the larger National Study.

Vermont has a notably low overall surgical rate, being at about the same level as the lowest of the four SOSSUS areas (area B). The overall surgical

rate for Vermont, as mentioned above, is 55 operations per 1,000 population per year and that of the four SOSSUS areas is 58, 74, 75 and 91. And yet the total number of board certified surgeons in Vermont is in the upper area of surgeon availability in the United States, being 27.0 board certified surgeons per 100,000 population as contrasted with 24.8 for the United States as a whole. The data for Maine show an overall surgical rate of 68.9 operations per 1,000 population per year. In Maine, the number of surgeons is slightly less than the national average (Maine 21.5, national 24.8). In these simple raw statistics therefore we find direct failure to corroborate the main conclusion of the authors. In Vermont there are many surgeons but few operations. In Maine there are relatively few surgeons but a normal number of operations. Why do the authors fail to omit this in their consideration?\*

Turning now to the incidence rates for specific operations displayed by these authors we find that some of the numbers are so small as to be vanishing in terms of any meaningful statistic. For example, several of the health service areas in Maine have a population of about 20,000 (the exact population of each health service area is not shown in the paper). We are therefore dealing with very small numerators in these surgical rates. The authors are considering as significant, the difference between 6 and 20 varicose vein operations, between 22 and 24 appendectomies, and between 70 and 120 herniorrhaphies. These are very small differences in terms of absolute numbers of patients. It is clear from the records of any hospital, community, or the activities of any surgeon, that differences like this are experienced between years with the happenstance coming and going of symptomatic disorders of this type. The same would be true between small area or small-time variations in other infrequent population events.

In the case of hemorrhoidectomy, considering the average size of the Vermont service areas (25,000 population) only six people would have had to alter their minds in the direction of injection treatment, to produce this "small area variations in health care delivery" from which the authors draw their conclusions. Why did the authors fail to examine the number of injection treatments of hemorrhoids, to contrast with operation, in order better to evaluate patient demand factors? Considering the incidence of hemorrhoidectomy in populations studied by SOSSUS (0.6 hemorrhoidectomies per 1,000 population per year) on the number of people seeking this operation in a population of 8,000, a threefold increase from 4 persons to 12 persons would be required before significance was reached. And even here, with a threefold increase, we are still dealing with tiny integers in the numerator: 4 and 12!

\*The example of Canada would also be germane. The number of surgeons is about the same as that in the United States yet the operation rate per 1,000 population in some of the provinces is extremely high, much higher than the United States. How would the authors explain this?

Examining the bar graphs (Figure 4 in the article on Maine) it is evident that there are variations around the statewide mean for total procedures. And yet, the reader will note that in the five areas studied, three are almost precisely at the state mean and the other two show variations of only about 25%. Stated otherwise, when one deals with enough events ("all surgical operations") the statistical problems inherent in analyzing the incidence of infrequent events (such as hemorrhoidectomy) in small populations, begin to disappear. The "small area health care variations" begin to diminish in importance or significance. In the statistical handling of the data from Maine, each of the chi square tests used by the authors compares a single region with the state as a whole. What about difference between regions? Are these significant? In many cases they are not.

Again, without going into great detail, comparison with the SOSSUS national data for much larger regions is interesting merely as an example of medical variability. In that National Study, considering the four areas, tonsillectomy varied from 2.0 to 5.6 procedures per 1,000 population per year, appendectomy varied from 1.0 to 1.7 operations per 1,000 population per year, prostatectomy varied from 0.6 to 1.1 operations per 1,000 population per year, hemorrhoidectomy from 0.6 to 0.8 and varicose vein operations from 0.4 to 0.8.

The authors then move on to some interpretation. They state that "Bunker has shown the incidence of common surgical procedures in the United States to be double that of the United Kingdom." The authors fail to mention the fact that in Bunker's study two procedures (adenoidectomy and circumcision) were more common in Great Britain than in the United States. They failed to mention the fact that appendectomy, cataract extraction and thyroidectomy were essentially equal in incidence in the two countries. They fail to mention the remarkable fact that in Great Britain appendectomy in women is commoner than in men and commoner than in the United States. The authors might derive some comfort from the fact that they are not alone in misquoting Bunker's data! Many speakers at health care symposia or congressional hearings make a habit of quoting from Bunker's study only those data that support their own theses, omitting completely mention of the rest.

The authors then indulge in some economic speculation. How much more would it cost if all populations had operations at the high rates? How much would be saved if all populations had operations at the lower rates? Such calculations while exciting to the legislator, are grossly misleading because there is no reason ever to expect or believe that all populations will seek or require care at the same level as either the highest or lowest sample cohorts within that population. One cannot possibly assume that care at the lowest level could, would, or should be spread over the whole population of any region, even in a very highly regimented socialist or

communist society. The cost figures, while appealing to economists, are therefore in point of fact very unrealistic because there is no way in which health care variations can be ironed out, denying the wish of patients for treatment or treating others who do not wish to be treated. Such estimates are therefore irresponsible. They give the authors an aura of social concern and economic planning when actually such conjectures are merely idle speculation.

Finally, we get back to the basic question asked at the beginning. Why did the authors fail to report the small area variations in obstetrical delivery? Why did they fail to show the data on fractures? Or burns? Or pancreatitis? Is it possible that they actually did carry out such studies, but found precisely the same sort of small area variations? Could it be that, realizing that those data would undermine their basic thesis that provider factors are solely responsible, they then simply omitted them from the publication?

Fortunately, we can answer one of these questions. We have recently completed a study of Maine. We have used six slightly larger health service areas that cover the entire state without omitting any regions, areas, counties or hospitals. We find that there is a variation amongst these areas in the rate of obstetrical delivery from 16.3 to 20.6 deliveries per 1,000 population. This cannot be regarded as due to "provider factors" unless the activities of physicians to secure obstetrical patients involve behavior patterns not ordinarily associated with surgeons and gynecologists.

In one of the Wennberg and Gittelsohn articles (Vermont) the statement is made that "obstetrician effort was more than ten times greater in some areas than in others." There is no further explanation of this remarkable statement. Since virtually all of the obstetrical deliveries in both Maine and Vermont are carried out by obstetricians, this huge difference in "obstetrician effort" must have something to do with differences in the incidence of pregnancy. How do the authors explain a ten-fold difference in pregnancy incidence between two of their so-called small areas? By way of comparison, the four national areas studied by SOSSUS showed a variation in obstetrical delivery rate from 14.8 to 16.7 per 1,000 population per year.

The same considerations apply to trauma, as mentioned previously. There is a markedly irregular distribution of the incidence of fractures and burns. In the SOSSUS study, for example, the incidence of open and closed reduction of fractures (i.e., total fractures) varied from 0.8 to 1.2 per 1,000 population per year over very large areas. This is a variation equal to 50% of the lower figure. Epidemiology of trauma is difficult to relate to "provider factors." The authors indicate that they have applied "age" corrections to their data. This makes the assumption that the age group distribution of a disease will be the same throughout a large area. This assumption is not always justified. Fractures in Maine would be an interesting example. Where there is a large ski de-

velopment, fractures will occur in a younger age group than in those areas where fractures are associated with farm labor and industrial activity including the construction trades. In any event, provider factors cannot be blamed for variations in the incidence of trauma. It is to be regretted that the authors did not include any examination of this phenomenon in their studies.

In summary, the picture presented by Wennberg and Gittelsohn, of physicians, surgeons and hospital administrators, seeking to influence demand and delivery of health care in the small areas of Vermont and Maine fails to be a convincing one. It is not supported by the articles in question, nor is it supported by common experience. Most important, any acquaintance with the actual conditions of practice of medicine and surgery in these two areas would demonstrate that capricious whim and "provider factors" do not operate the way the authors claim that they do. Although these intuitive disagreements are strong, they are not enough; it has been the purpose of this brief article to show some factual bases upon which such a disagreement might be based.

There is one added note concerning the social responsibility of sociologists who are studying health care delivery at this time. Anything and everything published in the literature will be taken up and quoted as authoritative, by legislators in con-

gressional hearings, and by their staff people. Both of the articles in question, have recently been quoted in Washington hearings by the Kennedy Committee and the Moss Committee. They have been used to prove that it is the capricious whim and fiscal motivation of surgeons that dictates the level of surgical care in the community, rather than the needs of the population. It is unfortunate that these two studies, uncontrolled as they are, and with such glaring deficiencies were published at all, and especially unfortunate that they now provide some additional basis for medical legislation of a national character.

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# The Authors Respond

We appreciate the opportunity provided by the Editor of responding to Dr. Francis Moore's<sup>1</sup> preceding critique of our two recent articles<sup>2,3</sup> on small area variations in the utilization of surgical procedures and other health services. The language "capricious whim of hospitals, physicians and surgeons" is strictly Dr. Moore's, never having been employed by either of us. Our point by point response is roughly in the order of Dr. Moore's critique:

## 1. Selection of procedures

Dr. Moore's allegation that we look only at procedures which fit our argument is not true. The basis for selection of procedures for analysis was relative frequency and the types of surgery previously reported in the literature, as mentioned in the text. There is simply insufficient space in a journal article to deal with the hundreds of distinct procedures codes in the medical record. As to Dr. Moore's specific objection to our failure to consider fractures and obstetrical delivery because the "data failed to support their thesis," we indeed have examined and published data on these two categories and they support the thesis admirably (Figure 1). The hospitalization rate for deliveries and other pregnancy related conditions in Maine<sup>4</sup> and Vermont exhibit low variability over neighboring areas (as Dr. Moore's own data for Maine and SOSSUS clearly show). This is to be anticipated: Unlike such European countries as Holland, obstetrical traditions in the United States call for hospitalized delivery; and the birth rate among neighboring areas is approximately the same.

By contrast, admissions for fractures<sup>5</sup> show intermediate variability. Physicians familiar with treatment of trauma will recognize that not all fractures are admitted to hospitals for care. Judgment as to which cases should be hospitalized (as judgment concerning which should be treated with closed or open reduction techniques) may vary from physician to physician.

## 2. Variation between years

Dr. Moore suggests that "variations between successive years might be just as great as the variations between local areas." Only one year of data was available at the time of writing, 1969 for Vermont and 1973 for Maine and it was not possible to study annual trends. Since publication, we have examined and reported on trends between and within areas.<sup>6,7,8,9</sup> The general pattern is a marked consistency within areas over time (as exemplified by Table 1). Tonsillectomy procedures<sup>8</sup> and cesarean section<sup>9</sup> provide notable exceptions. Over the five-year period 1969-73 for Vermont, the overall tonsillectomy rate has declined by 40%. The proportion of deliveries by cesarean section nearly doubled

in areas served by hospitals with fetal monitoring and remained fairly constant in areas served by community hospitals. Consistency is measured by the rank order correlation of areal rates at the beginning and end of the period and by the Kendall concordance coefficient.

## 3. Control information

Dr. Moore rightly points out that "control information" should be studied to provide meaningful comparison between areas. He undoubtedly is aware that only a limited amount of data is available by individual town from secondary sources including the U.S. Census. Indeed, we have examined a wide range of available socio-demographic variables in order to measure differences and similarities between areas. Based on Vermont vital statistics for the period 1968-72, one of us has prepared a report<sup>6</sup> on mortality differentials. In general, the 13 areas of Vermont exhibit low variability in total death rates, life expectation and cause specific mortality for such broad diagnostic classes as malignant neoplasms, heart disease, stroke and automobile accidents. Stillbirth, neonatal, perinatal and infant mortality rates similarly exhibit lower inter-area variability than all of the common surgical procedures except repair of inguinal hernia. In many instances, the vital events are of much lower frequency than the types of surgery under consideration. The latter should ease some of Dr. Moore's concern about rare events.

We also believe it is important to study comparative behavior in seeking medical care. An extensive household survey in six Vermont hospital service areas (including areas at the extremes in range of use of hospital and surgery) shows the populations to be well matched on socio-economic factors, including ethnic background, health insurance coverage and percent below poverty level; the distribution of reported illness and individual behavior in seeking care are similar. These studies, referenced in Maine I,<sup>3</sup> will be published in a subsequent issue of *The Journal of the Maine Medical Association*.<sup>10</sup>

## 4. Size of numerators

Dr. Moore need not fear that the importance of variations among small areas disappears because of "tiny integers in the numerators." He draws attention to our Figure 4.<sup>3</sup> The numerators for these rates are not small. The high and low rates for tonsillectomy are based on 652 and 1,042 cases, respectively. For the less common procedures, the high rate for hemorrhoidectomies is based on 94 cases, the low on 66. For varicose veins, the corresponding numbers are 60 and 65. Statistically, differences in rates between areas are highly significant. They are also of medical significance. For example, the number of hemorrhoidectomies in the high area ex-

Figure 1  
Pattern of Variation for Congenital Anomalies, Pregnancy  
Related Admissions and Four Common Pediatric Surgical Procedures

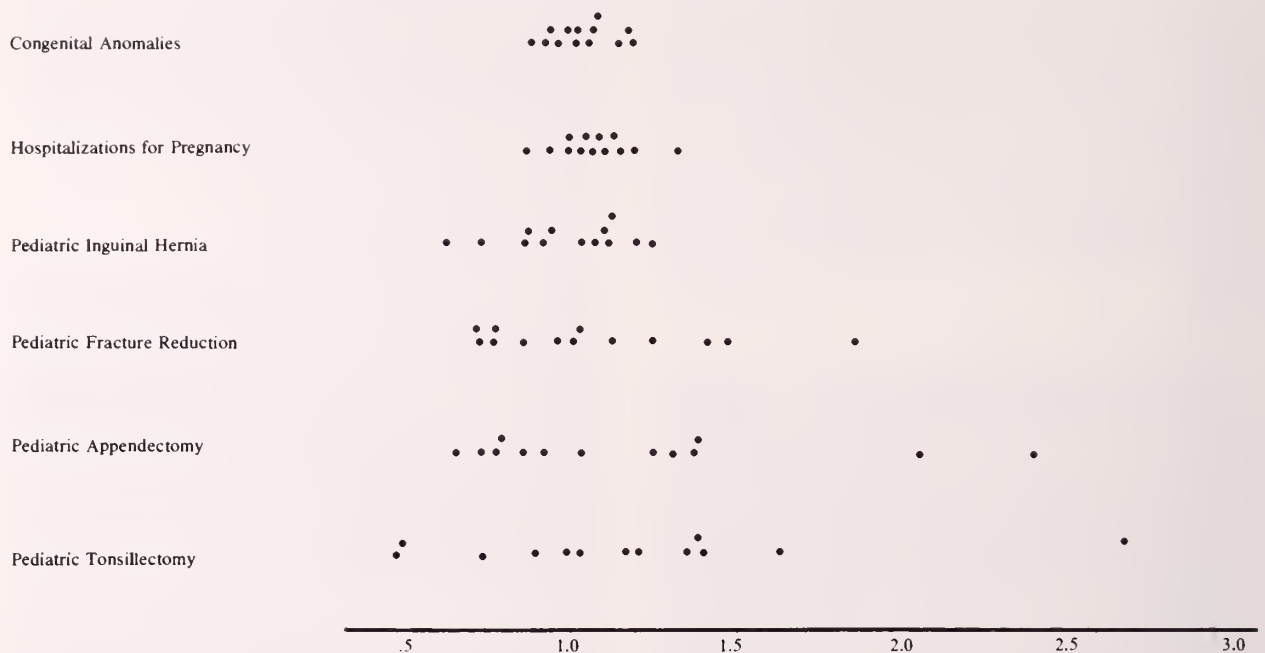


Figure 1 shows the ratio of the age-adjusted rate of admission to the state average rate for 13 hospital service areas. Admission for congenital anomalies and pregnancy associated conditions exhibit low variability. Of the four procedures, inguinal hernia shows low variability and none of the areas differ from the state average at the .01 level of significance. Fracture reduction demonstrates intermediate variability with four areas statistically different. Appendectomy and tonsillectomy show much greater variations. (The state average annual rate for congenital anomalies is 19 per 10,000; for conditions of pregnancy it is 189. The state average rate for the four procedures, in order, is 22, 55, 27, and 96 per 10,000 population per year. The data for pediatric procedures is for 13 Vermont hospital service areas and covers five years (1969-1973).<sup>5</sup> The data for congenital anomalies and pregnancy associated conditions is for the 13 largest Maine hospital service areas for the year 1973<sup>4</sup>.)

ceeds the expected number by 60. As Dr. Moore will recognize, many inferences about therapeutic effectiveness often are based on smaller numbers of cases.

##### 5. Age corrections

Dr. Moore remarks that the authors have applied "age" corrections to their data and have made the assumption that "the age group distribution of a disease will be the same throughout a large area." The first part of the statement is true and the second grossly false. As stated in the text, we have computed age adjusted rates using the direct method of adjustment which is standard demographic practice. Age adjustment is required because the conditions under study vary with age. The adjustment is applied to insure comparability between areas with differing age structures, a point which Dr. Moore has missed.

##### 6. Elective surgery

Excluding appendectomy, Moore rightly states that the other eight surgical procedures involve an important interaction between patient, physician and surgeon. He then goes on to remark that "to assume that alterations in herniorrhaphy repair are always related to 'provider factors' " is a gross

oversimplification. The statement errs badly in several major respects. We never made it. Had Dr. Moore looked at the data, he would have noted that herniorrhaphy, of all common types of surgery, exhibits the least variability between areas. Evidently, inguinal hernia, with its high apparency to the patient, is treated similarly across areas (See Figure 1). Dr. Moore's concluding 'platitudes' in the same paragraph "no psychiatrist, no psychoanalysis, no surgeon, no surgery" is well supported by the SOS-SUS study in which he is a participant. Although the SOSSUS report virtually ignores the issue," Dr. Moore's own data clearly demonstrate a higher incidence of surgery in the areas with the higher number of surgeons per capita (Figure 2).

##### 7. Population coverage

Dr. Moore, in his comments on population coverage, misrepresents the concept of a population rate, the most fundamental idea in epidemiology and demography. In the numerator of the rate, we require a complete count of the events occurring to the members of the population at risk constituting the denominator. Both of these conditions have been fulfilled in the Vermont and Maine studies, not to mention the Lewis<sup>12</sup> report on Kansas Blue Cross/Blue Shield subscribers which Dr. Moore also

TABLE 1

## PRIMARY APPENDECTOMIES AND VARICOSE VEIN STRIPPING IN TWO SMALL VERMONT HOSPITAL SERVICE AREAS\*

	Observed and Expected Number of Cases by Year					
	1969	1970	1971	1972	1973	All Years
Appendectomy						
Area 1						
Observed	29	34	37	46	31	177
Expected	22.1	20.7	21.1	19.5	19.7	103.1
Area 2						
Observed	14	15	22	17	11	79
Expected	22.5	21.0	21.9	20.1	19.9	105.4
Varicose Veins						
Area 1						
Observed	11	12	9	18	10	60
Expected	9.8	9.7	9.7	8.2	8.9	46.1
Area 2						
Observed	29	22	22	13	23	109
Expected	10.7	10.6	10.6	9.0	9.4	50.3

\*Population circa 10,000

The data are for two Vermont hospital service areas with populations of about 10,000 (1970 census). Area 1 has a high appendectomy rate, Area 2 a high rate of varicose vein procedures. The numbers are consistent between years. By the end of five years, Area 1 has about 75 more appendectomies than expected (based on STATE average); Area 2 has about 60 more examples of varicose vein stripping than expected.

criticizes. It is irrelevant whether or not the population of an entire state is covered. The issue is that all of the events under consideration be included in the numerator, a point explained in the text and in all basic works on epidemiology.

#### 8. Population size

We agree with Dr. Moore on the difficulty of drawing inferences about rare events in small populations. In part, this is a classical statistical problem accounted for directly in the standard deviations of the population rates. To argue that the four SOS-SUS study areas average about 1,000,000 persons and that the total surgical rates range narrowly between 58 and 91 is not relevant. Such information tells us nothing about intra-regional variability which is the central point of our two reports. Each hospital service area in Maine and Vermont is an aggregation of adjoining towns whose residents receive most of their hospital care primarily at local facilities. Most hospital service areas contain only one facility staffed by one group of physicians. An important thrust of our effort has been to study local differences in the delivery of care and to examine the relationships between morbidity, care, and community and provider characteristics. To lump the experience on a regional basis misses the entire point.

Dr. Moore should be well aware that major differences in the incidence of surgery exist between large population groups. For years, the Canadians have recorded rates for gynecological and abdominal surgery far in excess of those for the United States. Similarly, the rates in Great Britain and among members of group health plans in the United States are less than half those for subscribers of Blue Cross/Blue Shield type plans. Canadian cholecys-

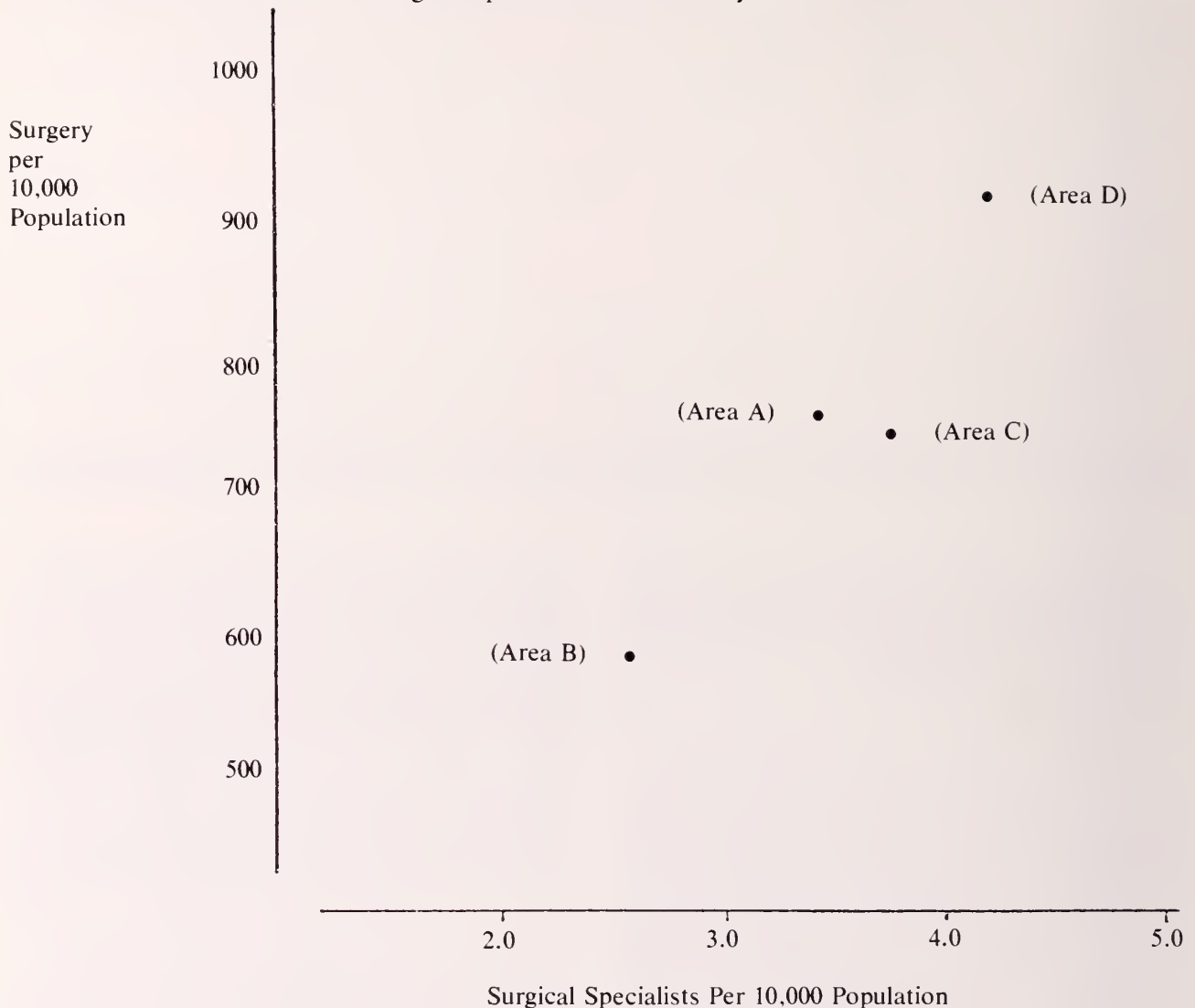
tectomy rates are more than five times the British rates. The West Germans experience remarkably high-appendectomy rates. It is clear that these differences between these areas, based on millions of persons, are real and statistically significant. In no instance has it been possible to relate variations in common surgery rates to variations in the incidence and prevalence of the conditions for which the surgery is performed. There is no evidence suggesting that group health subscribers have half as much gynecological disease as subscribers of other health insurance plans or that English females have significantly less cholelithiasis than Californians or that the incidence of acute appendicitis varies by a factor of 2 between blue and white collar workers in Hanover. By the same token, it should not be surprising that practice differences and similarities occur between neighboring Vermont or Maine communities served by different groups of physicians. In one area, served by a single hospital, over half the deliveries are induced while in another the cesarean section rate is about double that recorded in the rest of the State. The same situation pertains in varying degrees to the types of common surgery under discussion. The issue will not disappear by resorting to innuendo, ad hominums and distortion. Rather, the responsible approach is to study current practice and to ascertain which level of care results in betterment of the health, tranquility and general well-being of the population.

#### 9. International comparisons

Dr. Moore has misread our quote of the Bunker report<sup>13</sup> on the incidence of common surgical procedures in Great Britain and the United States. We have quoted Bunker accurately, directly and without error. Dr. Moore's allegation that we have sup-

Figure 2

Operations Performed and Supply of  
Surgical Specialists in Four Study Areas



Data is from Table 11, Chapter IV, *Surgery in the United States: A Summary Report of the Study on Surgical Services for the United States*. Sponsored Jointly by The American College of Surgeons and The American Surgical Association, 1975. There is a concomitant variation between surgeon supply and rate of surgery.

pressed similarities in appendectomy, cataract extraction, thyroidectomy and circumcision rates is beside the point; by the same token Dr. Moore has suppressed the 3 to 1 differential in cholecystectomy rates and the 2 to 1 differential in hysterectomy rates. It was not our intention to reproduce the Bunker article in full since it was published in a widely available journal.

#### 10. Social responsibility

In his concluding paragraph, Dr. Moore's gratuitous comment on the social responsibility of sociologists is not applicable. Neither of us has ever been a sociologist; one of us is a physician and the other is a biostatistician. Dr. Moore's term "uncon-

trolled studies" is correct only in the sense that all observational studies including SOSSUS are uncontrolled. The "glaring deficiencies" of our studies remain unknown to us, our colleagues or referees. We have attempted to insure that the data are correct within the limits imposed by the medical record and other data systems available to us. It has been our objective to let the data tell their own story. We feel gratified that our work has received national attention and regret that Dr. Moore finds the situation "especially unfortunate."

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#### COMMENT BY DOCTOR MOORE — (JANUARY 12, 1977)

I am delighted that Wennberg and Gittelsohn have been stimulated to present the obstetrical and fracture data. The obstetrical variation (0.9 to 1.4) and the fracture variation (pediatrics only, 0.6 to 1.8) — if we may interpolate from their graph — clearly indicates that "provider behavior" is not the only source of "small area variation in health care delivery" with which they are so concerned.

Unanswered remains the plea that they broaden their view and document small area variations in other social phenomena that reflect both local custom (fraction of registered voters voting, for example) or market forces (auto, television or refrigerator

sales, movie house attendance). Without this we are left with the message that medical variability is due to the behavior of doctors only, and the conclusion drawn by DHEW that the best way to cut costs is to reduce services.

For any "ad hominums" (sic) I apologize; but if these two authors are going to make a career of "small area variations"; let us hope these will put their studies on a sounder scientific basis. We all owe them a debt of gratitude for their concern about this especially difficult statistical and interpretive problem: local variability.

FRANCIS D. MOORE, M.D.

#### EOSINOPHILIC GRANULOMA OF BONE — Continued from Page 48

panied by rapid healing of the lesion.

In summary, eosinophilic granuloma of bone has a relatively benign prognosis when compared to the other reticuloendotheliosis. The microscopic pathology has been reviewed as well as the radiographic differential diagnosis and treatment modalities.

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DAVID E. SMITH  
COMMISSIONER

## Maine Department of Human Services

# Taxes, Cigarettes and the Health of Maine Citizens

EDWARD MILLER\*

### INTRODUCTION

There is no longer any serious controversy about whether or not cigarette smoking is dangerous to your health. Every pack of cigarettes sold in this country states this fact. Smoking is being uncovered as a cause or major contributing factor to a greater number of diseases each year (Appendix A). The costs of smoking to society go far beyond simply the expenses of medical care, rehabilitation and personal hardship.

Increased health, fire and life insurance premiums and higher costs of consumer goods due to increased absenteeism by smoking workers amount to billions of dollars annually and, with a few exceptions, these costs are passed on to the general public, smoker and non-smoker alike (Table 1). In simple economic terms, the revenue produced by cigarettes through taxation covers only about one-fifth of their cost to society. Government, both as a major payor of medical care costs and as a large employer, has a financial, as well as a human interest in keeping citizens healthy and in trying to reduce the health risks and lowered productivity of smokers.

Although most attempts to reduce smoking have been educational in nature and not overwhelming in their success, a number of changes in people's smoking behavior have occurred. Since the publication of the Surgeon General's Report on Smoking and Health in 1964, an estimated 30 million Americans have totally quit smoking, while millions of others have either tried to stop, reduced the number of cigarettes they smoke or changed to a brand lower in tar and nicotine, two of the most dangerous substances contained in cigarette smoke.

Since the risk of disease from smoking increases as the dosage of tar and nicotine increases, the gradual reduction of the average tar content per cigarette over the past twenty years may have had some effect on the smoking implicated death rate. The average cigarette today contains about 20 mgs. of tar as opposed to 36 mgs. of tar in 1954. While the percentage of adult male smokers has been declining,

### APPENDIX A

#### DISEASES ASSOCIATED WITH CIGARETTE SMOKING

##### CANCER

*Lung Cancer* — Cigarette smoking is the major cause of lung cancer,<sup>1</sup> which is now the most frequent cause of death from cancer among American men.<sup>2</sup>

*Cancer of the Larynx* — has been significantly and causally linked with cigarette smoking.<sup>3</sup>

*Cancers of the Buccal Cavity, the Pharynx, and the Esophagus* are strongly associated with smoking.<sup>4</sup>

*Cancers of the Urinary Tract — Kidney and Bladder*, has cigarette smoking as one of its contributory causes.<sup>5</sup>

*Cancer of the Pancreas* is associated with smoking.<sup>6</sup>

*Oral Cancer* has been found to be strongly associated with smoking.<sup>7</sup>

##### CARDIOVASCULAR DISEASES (Heart and Blood Vessels)

*Atherosclerosis* (Hardening of the Arteries) is almost certainly and significantly promoted by smoking.<sup>8</sup>

Smokers have an increased risk of having a myocardial infarction (heart attack) and of dying from coronary heart disease.<sup>9</sup>

Incidence of coronary heart disease among men aged 39-49 who smoke is three times the incidence among non-smokers.<sup>10</sup>

*Stroke* — Smokers have a higher incidence. Those who quit smoking return almost to normal rates.<sup>11</sup>

*Aortic Aneurysm* — is statistically associated with smoking.<sup>12</sup>

Those who quit smoking return to almost normal rates.<sup>13</sup> Smokers have aortic aneurysm death rates three times non-smokers in the 45-64 age range and five times among men over 65.<sup>14</sup>

##### PULMONARY DISEASES

*Pulmonary Emphysema* — is highly associated with cigarette smoking,<sup>15</sup> which is now considered the primary cause of this disease in man.<sup>16</sup>

*Chronic Bronchitis* — is caused primarily by cigarette smoking.<sup>17</sup>

*Decreased Lung Capacity* — not associated with specific disease has been reported among smokers.<sup>18</sup>

##### OTHER ILLNESSES

*Dangers During Pregnancy* — Maternal smoking is associated with low birthweight and higher perinatal death rates.<sup>19</sup>

For All References see: Appendix A

there has been an increasing number of teenagers and women who have begun to smoke (Table 2).

Recent estimates indicate that over ninety percent of all smokers are aware of the negative effect of smoking on their health. Since many smokers will not quit simply on the basis of "factual information," increasing the number of disincentives which will make smoking less attractive may be a feasible strategy to reduce the rising per capita consumption of cigarettes in Maine.

\*Health Education Program, Bureau of Health, Maine Department of Human Services and the Maine Lung Association.

TABLE 1

NATIONAL COST FACTORS OF SMOKING<sup>2</sup>

Cost of Higher Fire Insurance Premiums Due to Smoking-Caused Building Fire	\$ .2 billion
Cost of Smoking-Caused Forest Fires	.1 billion
Cost in Higher Prices of Consumer Goods Resulting from Smoking-Caused Absenteeism, etc., at \$4/per week/per smoking worker	8.0 billion
Cost of Higher Life Insurance Policies	.6 billion
Cost of Higher Health Insurance Policies	.5 billion
Cost in Public Cleanup, Public Health, Higher Auto Insurance, Cigarette Damage to Public Buildings	not available
Cost of Illness and Death Due to Cigarettes	5.0 billion
Total Costs from Above Sources (National)	\$14.4 billion*
(Maine Est.)	\$ 7.2 million

\*This figure does *not* include the \$11 billion spent nationally by people on the purchase of cigarettes each year.

TABLE 2

NATIONAL FIGURES ON SMOKING INCIDENCE  
PERCENTAGE OF CURRENT REGULAR CIGARETTE SMOKERS  
BY AGE AND SELECTED YEARS

	Teenagers <sup>3</sup>					
	12-13-14		15-16		17-18	
	Boys	Girls	Boys	Girls	Boys	Girls
1968	2.9	.6	17.0	9.6	30.2	18.6
1970	5.7	3.0	19.5	14.4	37.3	22.8
1972	4.6	2.8	17.8	16.3	30.2	25.3
1974	4.2	4.9	18.1	20.2	31.0	25.9
<i>Adults</i>						
(17 and over)						
	MALES			FEMALES		
1955 <sup>4</sup>	57 %			28 %		
1966 <sup>4</sup>	51 %			34 %		
1970 <sup>5</sup>	43 %			31 %		
1976 <sup>6*</sup>	39.3%			28.9%		

\*Data for 1975 is based on adults over 21 years of age.

TABLE 3

MAINE  
HISTORICAL CIGARETTE TAX DATA FOR THE STATE OF MAINE SINCE 1950  
FIRST CIGARETTE TAX ENACTED IN 1941

YEAR	RATE (CENTS)	DATE CHANGED	NET STATE CIGARETTE TAX COLLECTIONS (In Thousands of Dollars)	PER CAPITA SALES (PACKS)
1950	4		4,680	134.5
1951	4		4,508	128.6
1952	4		4,667	133.7
1953	4		4,784	138.0
1954	4		4,578	133.7
1955	4		4,607	133.3
1956	5	7/1/55	5,588	128.3
1957	5		5,759	128.0
1958	5		5,903	129.7
1959	5		6,188	135.5
1960	5		6,551	141.8
1961	5		6,859	145.9
1962	6	7/1/62	8,065	139.3
1963	6		8,043	138.4
1964	6		7,854	137.4
1965	6		8,011	139.1
1966	8	7/1/65	10,461	135.1
1967	8		10,429	136.0
1968	9-10	7/1/67-11/1/67	12,424	135.6
1969	12	6/1/69	13,150	135.2
1970	12		14,742	128.5
1971	12		15,541	133.2
1972	14	7/1/71	18,734	136.5
1973	14		19,438	138.0
1974	14		19,992	142.1
1975	16	7/1/74	22,975	140.7

"Statistical analysis shows that there is a consistent negative correlation between State cigarette tax rates and per capita sales of cigarettes over the years. This means that the higher the tax rate, the lower the sales . . . and, presumably, the consumption of cigarettes. . . . It would appear that increasing the State cigarette tax is not only a method of raising revenue but also a technique for discouraging cigarette smoking."<sup>1</sup>

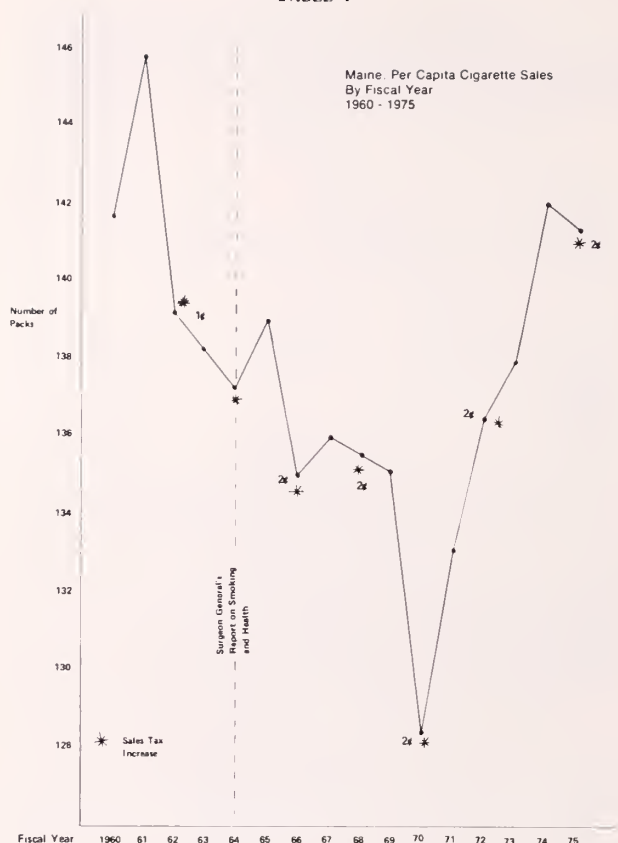
The following data is presented in support of actions necessary to significantly raise the State cigarette tax and, thereby, to reduce per capita con-

sumption, to ease the economic burden of smoking on Maine's taxpayers, smokers and non-smokers alike; and, most importantly, to reduce the number of Maine citizens who die or are disabled each year unnecessarily as a result of diseases associated with cigarette smoking.

TAXATION, PER CAPITA SALES  
AND TAX REVENUE

The following facts are presented as background information on taxation and per capita cigarette sales in Maine (see Tables 3 and 4).

TABLE 4



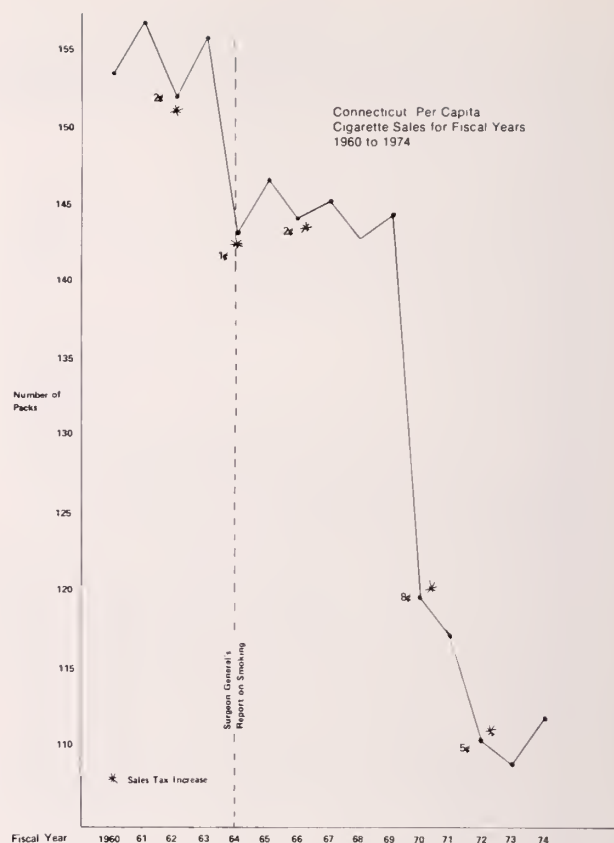
- Maine has never increased the tax on cigarettes more than \$.02 at any one time since the taxing of cigarettes began in 1941.
- Per capita sales of cigarettes in Maine has been increasing sharply since fiscal year 1970.
- Per capita sales in Maine in FY 1974 was 11% higher than in FY 1970 and was the highest it has been since FY 1961, three years before the Surgeon General's Report on Smoking and Health.
- Current Maine State Tax on cigarettes is 16c per pack. This was instituted on July 1, 1974.

The states of Massachusetts and Connecticut currently have the nation's highest state tax on cigarettes; 21c per pack. Between FY 1969 and FY 1972, Connecticut twice increased their cigarette tax. First from 8c per pack to 16c per pack then from 16c per pack to 21c per pack. The effects of the two most recent tax increases in Connecticut were rather dramatic. (See Table 5) In FY 1969, when Connecticut raised the cigarette tax from 8c per pack to 16c per pack, the following changes over the previous year took place:

- A 17% reduction in per capita sales (144.7 packs per person to 120.0 packs per person).
- A 66% increase in net cigarette tax collections (from \$34.6 million to \$57.3 million, an increase of \$22.7 million).

In FY 1971 when Connecticut raised the cigarette

TABLE 5



tax from \$.16 per pack to \$.21 per pack, the following changes over the previous year took place:

- A 6% drop in per capita sales (from 117.6 packs per person to 110.8 packs per person).
- A 23% increase in net State cigarette tax collections from \$56.5 million to \$69.3 million (an increase of \$12.7 million).

Recent cigarette tax increases in Maine, although not quite as dramatic as those in Connecticut, are presented below.

In FY 1970 when the Maine State cigarette tax was increased from 10c per pack to 12c per pack, the following changes over the previous year took place:

- A 5% per capita sales decrease (from 135.2 packs per person to 128.5 packs per person).
- A 12% increase in the net State cigarette tax collections from \$13.1 million to \$14.7 million (an increase of \$1.6 million).

In FY 1972 when the Maine State Cigarette Tax was increased from 12c per pack to 14c per pack, the following changes over the previous year took place:

- A 2% increase in per capita sales (from 133.2 packs per person to 136.5 packs per person). Although this seems like a poor result, the increase in per capita sales during the previous fiscal year (FY 1971) was 5.4% higher than FY 1970, 125.7 packs per person to 132.5 packs per person.

TABLE 6

**RESULTS OF A 5c OR GREATER TAX INCREASE BY STATE  
(FOR FISCAL YEARS 1950-1974)<sup>7</sup>**

State	Tax Increase Per Pack	Change in Net State Tax Revenue		% Change in Per Capita Sales
		Millions of \$	% increase	
	(12.25)			
Ark.	5.5c (17.50)	\$+ 8.0	+ 30%	0%*
Colo.	5c (5-10c)	\$+15.8	+103%	- 4%
Conn.	8c (8-16c)	\$+22.7	+ 66%	-17%
Fla.	7c (8-15c)	\$+10.6	+ 17%	- 3%
Minn.	5c (8-13c)	\$+ 1.3	+ 4%	- 1%
Neb.	5c (8-13c)	\$+ 6.1	+ 45%	- 3%
N.J.	5c (14-19c)	\$+30.4	+ 22%	- 6%
N.Y.	5c (5-10c)	\$+32.8	+ 27%	- 2%
Ohio	5c (5-10c)	\$+21.7	+ 13%	- 3%
Okla.	5c (8-13c)	\$+ 3.1	+ 14%	- 4%
Ore.	5c (4-9c)	\$+10.9	+ 57%	- 3%
Pa.	5c (8-13c)	\$+39.9	+ 35%	- 7%
R.I.	5c (8-13c)	\$+ 4.0	+ 40%	-18%
Tenn.	5c (8-13c)	\$+ 1.5	+ 5%	- 2%
Wash.	5c (11-16c)	\$+11.2	+ 30%	- 9%
W. Va.	5c (7-12c)	\$+ 8.6	+ 61%	- 3%

\*Represents a decreasing rate of change over previous fiscal year.

— A 21% increase in net State cigarette tax collections from \$15.5 million to \$18.7 (an increase of \$3.2 million).

In FY 1975 when the Maine State Sales Tax was increased by 2c from 14c per pack to 16c per pack, the following changes over the previous year took place:

— A 1% decrease in per capita sales from 142.1 packs per person to 140.7 packs per person. Again, this may seem to be a poor result but the increase in per capita sales during the previous fiscal year (FY 1974) was 3% higher than FY 1973.

— A 15% increase in net State cigarette collections from \$19.9 million to \$23.0 million (an increase of 3.1 million).

Using the projections from the Connecticut experience in 1971 when the State's cigarette tax increased from 16c per pack to 21c per pack, Maine could expect the following changes: A 5c per pack increase:

A 6% drop in capita sales over the previous year (from 140.7 packs per person to 132.3 packs per person which would be the lowest per capita sales since FY 1970).

A 23% increase in net State cigarette tax collections over the previous year. This would amount to a change from \$23 million to \$28.3 million (an increase of \$5.3 million).

#### SUMMARY

Yearly per capita sales of cigarettes in Maine have been rising rapidly and steadily since 1970. This increase implies a future rise in the incidence of fatal or chronically disabling diseases in the Maine population, since many of the health-related effects of smoking such as heart disease, lung cancer, emphysema and chronic bronchitis, are not

seen for many years. This rising rate of consumption of cigarettes has been slowed down only twice since 1970. In each of these cases, a 2c per pack tax increase was enacted at the beginning of the fiscal year in which the decrease in per capita sales was noted.

When substantial tax increases (i.e., 5c or greater per pack) in other states have been enacted, in all but one case, a decrease in per capita sales of between 1% and 18% (the average is 5%) occurred over the previous year's sales.\* Increases in Net State Revenue from the cigarette tax hikes ranged from 5% to 103% with the average state showing a 36% increase over the previous year's net revenue (See Table 6).

No state has ever increased their cigarette tax more than 8c per pack at any one time; therefore, predictions on what would happen if Maine were to increase the tax 10c per pack, 25c or even 50c are purely theoretical. There would probably be a point of diminishing returns beyond which any further increases in the tax would have little, if any, effect on reducing sales or consumption. In addition, a severe drop in per capita sales without a substantial increase in taxes, would begin to decrease tax net revenue.

Maine can be reasonably assured that any substantial increase in the State cigarette tax will have two effects. First, there will be an increase in the net tax revenue collected. Second, there will be a drop in per capita sales, or at least a slowing down effect on per capita sales, which are now reaching all time highs.

One of the most common arguments against a cigarette tax increase, aside from the obvious negative reaction to be expected from the tobacco in-

\*In this one case, the per capita sales increased at a decreasing rate.

dustry, is the possibility of bootlegging lower priced cigarettes into the State of Maine. In a September 1975 article in *The New Englander*, this topic was addressed and concluded that Maine . . . "is protected from smugglers by distance, low population density and the more lucrative markets to the south."<sup>8</sup>

These more attractive markets include the large and densely populated urban areas in Massachusetts and Connecticut (eg., Boston, Hartford, New Haven, Worcester) where the current cigarette tax is 21c per pack and where it is much more cost-effective to bootleg. Maine could probably raise their State tax even higher than Connecticut and Massachusetts and still not suffer greatly because of the geographical and demographical barriers to large scale bootlegging. Levitt has found that "the evidence seems to be against the sales migration hypothesis, and in favor of the view that an increase — especially a substantial increase — acts as a deterrent to cigarette smoking."<sup>9</sup>

Another common argument against a cigarette tax increase is that it is regressive and places an unfair burden on the poor. An alternative to an across the board increase in cigarette taxes is currently being used in New York City. By taxing cigarettes according to their tar and nicotine content, not only can some of the risks of smoking be slightly reduced, but the tax is levied in a much less regressive manner since citizens (poor and rich) still have the choice of which brand to smoke.

As of this date, New York City is the only location in the country using this approach to taxation. Model legislation and assistance in its implementation is available from a variety of sources.<sup>10,11</sup> Projected revenue derived from this type of approach in Maine would be as follows:<sup>12</sup>

Per Pack Tax Rate Increase*	Revenue per Million Population (in millions of dollars)		
	Low Estimate	Medium Estimate	High Estimate
0.2c,3c	3.0	3.2	3.4
0.3c,4c	3.9	4.2	4.5
0.5c,6c	5.6	6.2	6.8
0.9c,10c	8.5	9.9	11.1

\*The three figures represent the tax on cigarettes with low, medium, and high nicotine, and tar contents in that order.

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## Pharmacology and Clinical Use of Drugs in Hypertensive Emergencies

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### ABSTRACT

Hypertensive emergencies are life-threatening situations that require prompt reduction in blood pressure. The selection of the appropriate hypotensive agent is dependent upon careful review of the patient's cardiovascular status, consideration of the urgency of the clinical situation, and the pharmacologic properties of the therapeutic agents available. Rational selection based on these factors should result in satisfactory blood pressure control with limited morbidity and mortality.

A marked or sudden elevation in blood pressure to a severely hypertensive level, regardless of the etiology, constitutes a life-threatening situation and requires prompt intervention. A decrease in blood pressure will generally diminish or nullify the likelihood of irreversible damage to the heart, brain and kidney.<sup>1,2</sup> This report discusses the clinical pharmacology and appropriate choice of antihypertensive agents useful in the treatment of hypertensive emergencies.

### HYPERTENSIVE EMERGENCIES: CLINICAL CONSIDERATIONS

Life-threatening, often acute, elevations in blood pressure may occur in the course of any hypertensive disease, including acute glomerulonephritis, chronic renal disease, renovascular hypertension, toxemia of pregnancy, collagen vascular disease, pheochromocytoma, or intake of catecholamine precursors while concomitantly ingesting monoamine oxidase inhibitors.<sup>3,4</sup> The most common setting for a hypertensive emergency is during the accelerated phase of poorly-controlled, long-standing essential hypertension.<sup>4,5</sup>

Hypertensive crises are seen most often in patients aged 40 to 60 years who have had hypertension of 2 to 10 years duration. The incidence among such patients ranges from 1 to 7 percent.<sup>6</sup> In those with acute elevations of arterial pressure, the risk of complications is greater at any given level of blood pressure than in those with long-standing hypertension.<sup>4</sup>

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The consequences of a sudden elevation of blood pressure generally involve the brain, heart and kidneys. Complications include encephalopathy, cerebrovascular accidents, myocardial ischemia or infarction, left ventricular failure, and renal failure. Treatment of the hypertensive crisis will usually prevent or reverse many of these consequences.<sup>1,2</sup>

Lowering of blood pressure improves cerebral function as a result of vascular dilation and improved cerebral blood flow.<sup>7,8</sup> However, the extent of blood pressure reduction is a crucial variable. If blood pressure is reduced to hypotensive levels, cerebral function may actually be further impaired.<sup>3</sup> The antihypertensive agent should be one that can be easily titrated to obtain the desired blood pressure response with minimal risk of hypotension.

Hypertensive emergencies may be accompanied by intractable angina, left ventricular failure or myocardial infarction. Most hypotensive agents, by virtue of lowering peripheral vascular resistance, will improve myocardial function.<sup>9</sup> However, lowering of peripheral vascular resistance may be accompanied by reflex sympathetic stimulation that can increase myocardial work and possibly worsen cardiac manifestations. In this setting an agent should be selected that produces minimal reflex sympathetic stimulation; alternatively, the drug can be used together with another agent that antagonizes sympathetic activity.

Acute reduction in blood pressure is usually accompanied by a decrease in renal blood flow and glomerular filtration rate, often reflected by an increase in blood urea nitrogen or creatinine.<sup>2,10</sup> In patients with greatly impaired renal function, even a slight reduction in glomerular filtration rate may require that the patient be supported by dialysis. Accordingly, it appears appropriate to employ agents that maintain renal blood flow and glomerular filtration rate in this situation. It is also prudent to produce a gradual stepwise lowering of blood pressure rather than an abrupt fall to normotensive levels. This approach provides a greater opportunity for vascular lesions to heal with eventual improvement in renal hemodynamics.<sup>3,10</sup>

### MANAGEMENT OF HYPERTENSIVE EMERGENCIES

Once the diagnosis of a hypertensive emergency is made, the patient should be hospitalized, in an

intensive care unit. Hospitalization removes the patient from a stressful environment, and assures adherence to a prescribed regimen. Bed rest alone often produces a lowering of blood pressure as a result of decreased blood volume.<sup>11</sup> Diagnostic studies other than hemogram, urinalysis, serum creatinine and electrolytes, chest and abdominal x-rays, and electrocardiogram may be deferred until blood pressure is controlled.<sup>4</sup> Treatment should begin promptly, and adequate blood pressure reduction achieved within a few hours to a few days.

Diuretic therapy should be initiated together with antihypertensive therapy to antagonize sodium and fluid retention associated with treatment.<sup>12,13</sup> Diuretics also produce a blood pressure reduction by themselves, probably mediated by volume depletion and arteriolar dilator activity.<sup>14,15</sup> Volume depletion is of greatest significance after acute administration. The choice of a diuretic agent depends in part upon renal function. If renal function is normal, a thiazide diuretic may be adequate, but if azotemia is present, furosemide is preferable.<sup>16,17</sup> Some recommend that the goal of diuretic therapy should be to maintain a urine output of greater than one and one-half liters per day.<sup>18</sup>

The mode of administration of antihypertensive agents in hypertensive emergencies should be parenteral. Intravenous bolus, intramuscular injections or constant intravenous infusions may be employed. Intravenous bolus and intramuscular injections have the advantage of not requiring constant bedside monitoring, but precise titration of blood pressure may be impossible. Constant infusions of antihypertensive agents allow a controlled hypotensive response, but constant bedside monitoring is required. Regardless of the drug or mode of administration, the patient must be closely monitored.

#### SPECIFIC ANTIHYPERTENSIVE AGENTS

*Diazoxide* (Hyperstat<sup>®</sup>) is a potent and rapidly-acting hypotensive agent of demonstrated effectiveness in most types of hypertensive emergencies.<sup>2,19-23</sup> Diazoxide is a benzothiadiazine derivative related chemically to the thiazide diuretics, but without chloruretic and natriuretic activity.

Diazoxide exerts its antihypertensive effect by direct vasodilator action on the peripheral arterioles.<sup>19,24-26</sup> It has no significant effect on the venous circulation.<sup>27</sup> The precise mechanism of arteriolar dilation is uncertain, but the drug may interfere with calcium-dependent activation of the contractile process in vascular smooth muscle, either by blocking calcium receptors, depleting the intramuscular calcium pool, or inhibiting the release of calcium from such a pool.<sup>28,29</sup> The net effect of the vasodilator action is to lower peripheral vascular resistance, systolic and diastolic blood pressure. This is accompanied by increases in heart rate, cardiac output, left ventricular ejection rate, and stroke volume, all of which are mediated by reflex sympathetic stimulation.<sup>25,30,31</sup> The increase in cardiac

work may be undesirable in patients with limited cardiac reserve or atherosclerotic heart disease.<sup>19,21,32</sup> Orthostatic hypotension is not usually a problem,<sup>20</sup> but patients who have been treated with sympathetic antagonists such as reserpine or guanethidine, or who have undergone vigorous diuresis with concomitant volume depletion, may experience orthostatic blood pressure changes or an exaggerated response to diazoxide.<sup>33</sup>

The immediate effects of diazoxide on renal function are a reduction in renal plasma flow and glomerular filtration, both of which are usually reversed within hours.<sup>19,34,35</sup> Persistent reduction in sodium excretion also occurs, possibly mediated by intrinsic sodium-retaining properties of the drug, or by proximal tubular sodium reabsorption.<sup>34-36</sup> This emphasizes the need for concurrent administration of a diuretic.

Diazoxide is widely distributed to body tissues. The apparent plasma half-life of the drug ranges from 10 to 31 hours and is slightly increased in patients with renal disease.<sup>37</sup> Diazoxide is eliminated primarily by renal clearance of the unchanged drug, with hepatic biotransformation to the hydroxymethyl and carboxy derivatives being of minor importance.<sup>38</sup> Diazoxide is about 90% bound to one major site on human albumin;<sup>37</sup> this probably accounts for the slow rate of decline of total drug levels in plasma.

The intensity and duration of the hypotensive effect of diazoxide depends on the rate of infusion and the severity of hypertension.<sup>23</sup> High concentrations of unbound drug in the arteriolar blood are necessary to produce maximal arteriolar dilation. Slow rates of infusion produce minor reductions in blood pressure due to rapid and extensive protein binding.<sup>23,29</sup> For maximal hypotensive effectiveness, diazoxide should be administered by direct intravenous injection in a dosage of 30 mg (or about 5 mg/kg) over a period of 10 seconds or less. The onset of hypotensive effect occurs within one to five minutes, and the peak action within 2 to 5 minutes of administration. This is followed by a slight elevation that remains below control levels.<sup>19,20,25,37</sup> This second phase of blood pressure reduction persists an average of three to six hours, but has been reported to last up to 72 hours.<sup>20</sup> If a satisfactory hypotensive response is not observed in 30 minutes, a second injection should be given. The patient should be recumbent for at least 30 minutes after therapy with diazoxide, and blood pressure should be monitored every five minutes during this period. Rarely, hypotensive episodes may occur which may initially be treated by elevation of the legs or, if necessary, by norepinephrine infusion. Repeated doses of diazoxide may be required to maintain blood pressure control. Up to 1200 mg may be given in 24 hours.<sup>20,21,33</sup> A diuretic *must* be administered concomitantly or prior to the infusion of diazoxide to overcome its potent antinatriuretic effect. Once a satisfactory blood pressure response has been ob-

tained, oral antihypertensive therapy should be initiated to sustain blood pressure control.

The most common side effects of intravenous diazoxide include nausea, abdominal discomfort, sodium and water retention with precipitation of congestive heart failure after repeated injections (particularly in uremic patients) and a sensation of warmth or burning along the vein associated with extravasation of this highly alkaline drug. Postural hypotension, substernal chest pain simulating angina pectoris as well as the precipitation of angina pectoris, transient myocardial and cerebral ischemia during maximal hypotension, flushing, drowsiness, weakness, mild tachycardia, weight gain, and interruptions of labor in obstetric patients have also been observed.<sup>18-23,32,33,40,42</sup> The hyperglycemia that usually occurs following injections of diazoxide lasts no more than 12 hours and requires no treatment. However, blood glucose levels should be monitored especially in diabetics, uremics, and patients requiring multiple injections. Adjustments in insulin dosage may be required in diabetics.<sup>19,21,33,40</sup> Hyperuricemia occurs after diazoxide infusions and is related to decreased tubular secretion of uric acid.<sup>34-41</sup> Other unusual reactions include extrapyramidal effects,<sup>43</sup> and hypersensitivity reactions including skin rashes, fever, leukopenia, and thrombocytopenia.<sup>40</sup> Patients with known sensitivity to thiazide diuretics should not be given diazoxide.

*Sodium Nitroprusside* (Nipride®) is a potent, rapidly-acting hypotensive agent that has been known for years, but has only recently become commercially available for use in hypertensive emergencies. Sodium nitroprusside relaxes all vascular smooth muscle independent of autonomic innervation.<sup>44-49</sup> The cellular mode of action has not been established. The hypotensive effect is probably due to the action of the nitroso substituent in the nitroprusside radical.<sup>47</sup> This nitroso group has been shown to be 500 to 1000 times more potent as a vasodilator than the closely related nitrite.<sup>50</sup>

The hypotensive effect of sodium nitroprusside is extremely short, lasting approximately 1 to 2 minutes after stopping an infusion.<sup>46,49,53</sup> This is attributed to conversion of the active radical to inactive cyanogen, after interaction of the ferrous ion in nitroprusside with sulfhydryl groups in the red blood cells and tissues.<sup>47</sup> Hepatic rhodanese then converts cyanogen to thiocyanate. Thiocyanate appears to be oxidized back to cyanide by thiocyanate oxidase present in erythrocytes, with an equilibrium existing between the two compounds in favor of thiocyanate.<sup>52</sup>

Sodium nitroprusside, by producing both arteriolar and venous dilation, leads to decreased systemic vascular resistance and a decreased venous return,<sup>31,44,51</sup> finally resulting in a reduced stroke volume and cardiac output.<sup>31,44,53</sup> The fall in arterial pressure activates baroreceptor reflexes causing a 20 to 30% increase in heart rate.<sup>31</sup> Renal vascular

resistance decreases about as much as arterial blood pressure, causing renal blood flow and glomerular filtration rate to remain constant in many hypertensives. In some patients, however, renal blood flow may fall substantially.<sup>44,54</sup> The reduction in blood pressure is accompanied by an increase in plasma renin.<sup>54</sup>

Sodium nitroprusside reduces blood pressure within seconds after intravenous therapy is initiated. Because of extremely rapid clearance, sodium nitroprusside must be administered by constant intravenous infusion. Effective infusion rates range from 0.3 to 8.0  $\mu\text{g/kg/min}$ , but the rate must be adjusted to the individual patient.<sup>48,49</sup> The highest reported infusion rate is 800  $\mu\text{g/min}$ .<sup>55</sup> Infusions of nitroprusside should be initiated at a rate of 0.5  $\mu\text{g/kg/min}$ , and titrated until the desired hypotensive response is obtained. A constant-rate infusion pump is desirable, but not strictly necessary if adequate safeguards are taken. Sodium nitroprusside is light sensitive and therefore should be shielded from light with foil while it is hanging. Solutions that appear dark brown or blue in color should not be used. Infusions should be prepared in dextrose 5% in water and discarded after four hours.

Oral hypotensive therapy should be initiated as soon as possible after the blood pressure is in the desired range. Efforts should be directed at weaning the patient off sodium nitroprusside infusion after starting oral hypotensive therapy.<sup>56</sup>

Sodium nitroprusside is relatively nontoxic. Hypotension is of major concern, and requires constant bedside monitoring. If hypotension occurs, it can be reversed within minutes by stopping the infusion.<sup>46,49,53</sup> Most patients experience no symptoms during short-term sodium nitroprusside infusions. Occasionally, nasal stuffiness, increased body warmth, dizziness, weakness, muscle twitching, and nausea may occur.<sup>49,53</sup> These appear to be related to the infusion rates.<sup>53</sup>

Prolonged infusion of nitroprusside in patients with renal insufficiency may cause thiocyanate toxicity due to accumulation of this metabolite.<sup>47,57-59</sup> Manifestations may include weakness, nausea, tinnitus, psychosis,<sup>60</sup> and hypothyroidism.<sup>59</sup> Thiocyanate blood levels should be monitored in patients undergoing prolonged therapy. If levels exceed 12  $\mu\text{g/ml}$ , nitroprusside should be discontinued.<sup>47,59</sup>

*Hydralazine Hydrochloride* (Apresoline®) has been employed successfully in the treatment of hypertensive emergencies.<sup>61-63</sup> Its hypotensive action results from direct relaxation of the smooth muscle of the peripheral arterioles.<sup>61,64,65</sup> The vasodilation appears to be selective, being greater in the splanchnic vascular tree and renal vessels than in muscle and skin vasculature.<sup>66</sup> Accompanying the vasodilation and reduction in blood pressure is an increase in cardiac output, stroke volume, and heart rate, mediated by reflex sympathetic activity.<sup>61,67-69</sup> The increase in cardiac work as a result of reflex stimula-

tion has been associated with precipitation or exacerbation of angina pectoris, suggesting that hydralazine should not be used alone in patients with cerebral hemorrhage, because vasodilation and increased stroke volume may exacerbate this condition. The administration of hydralazine produces an increase in renal blood flow apparently independent of the increase in cardiac output, thus making it a preferred agent in patients with decreased renal function.<sup>62,67-69</sup> Hydralazine indirectly increases plasma renin activity by reflex stimulation of sympathetic receptors.<sup>70</sup>

The hypotensive effect of hydralazine correlates with its plasma level.<sup>71</sup> After oral administration, a substantial portion of a dose fails to reach the systemic circulation because it is biotransformed prior to reaching the circulation (first-pass effect). The extent of first-pass metabolism depends in part upon the genetically-determined acetylator phenotype.<sup>72</sup> Rapid acetylators may require up to 58 percent more hydralazine to achieve adequate hypotensive plasma levels than do slow acetylators.<sup>71</sup> The acetylator phenotype is less important after parenteral administration of hydralazine.<sup>22</sup> Similar plasma levels are obtained, and similar plasma half-life values (ranging from 2.0 to 7.8 hours) are observed, in slow or fast acetylators, suggesting that other mechanisms contribute to the clearance of hydralazine.<sup>72</sup> Plasma levels and half-life of hydralazine are increased in patients with renal insufficiency, suggesting that plasma level determinations might be useful in titrating dosage.<sup>71</sup>

In the treatment of hypertensive emergencies, hydralazine should be administered parenterally in a dosage of 10 to 20 mg, and repeated as necessary. The onset of its hypotensive effect occurs within 10 to 30 minutes, and its duration of action ranges from 3 to 9 hours.<sup>3,53</sup> The dose and frequency of administration necessary to control blood pressure are variable. The delayed onset and prolonged duration of action present difficulties in titration. Sodium and water retention may occur, but can be overcome by the administration of a diuretic.<sup>62,68</sup> Propranolol may be given together with hydralazine to block cardiac manifestations of reflex sympathetic activity.<sup>73-75</sup> Once the desired blood pressure response is achieved, oral hydralazine may be administered in equivalent doses. An oral dose of 75 mg produces about the same plasma levels and clinical response as 20 mg parenterally.<sup>72</sup>

Adverse effects include tachycardia, palpitations, headache, precipitation of myocardial ischemia, and flushing. These are related to reflex stimulation of the sympathetic system,<sup>61-63,69</sup> and can generally be prevented by administration of propranolol.<sup>73-75</sup> Hydralazine can also lead to a syndrome resembling systemic lupus erythematosus.<sup>76,77</sup> This syndrome occurs in 10 to 20% of patients treated with daily doses of 400 mg or more, but only rarely with doses of 200 mg or less. It probably has an immunologic basis, and is usually associated with cir-

culating antinuclear antibodies. Appearance of the "hydralazine lupus syndrome" requires that hydralazine be discontinued. Gastrointestinal intolerance, drug fever, skin eruptions, and peripheral neuropathies may also occur.<sup>78</sup>

*Trimethaphan Camsylate* (Arfonad<sup>®</sup>) competitively inhibits the action of acetylcholine at postganglionic nerve terminals and prevents postsynaptic depolarization by "stabilizing" the membrane.<sup>79,80</sup> This agent has no effect on preganglionic acetylcholine release, cholinesterase activity, or postganglionic catecholamine release, nor does it have any direct action on vascular smooth muscle.<sup>79,80</sup>

Accompanying the hypotensive effect are reductions in cardiac index, left ventricular ejection rate and cardiac output.<sup>31,81</sup> A rise in cardiac output may be seen in hypertensive patients with decompensated heart failure or mitral valve disease.<sup>81</sup> These actions are probably due to a reduction in venous return. An insignificant reflex increase in heart rate is usually observed, probably resulting from incomplete autonomic blockade.<sup>31,79,81</sup> Decreased coronary vascular resistance has been demonstrated, though the effect on coronary blood flow is variable.<sup>81,82</sup> Cerebral vascular resistance and blood flow generally decrease.<sup>81</sup> Renal blood flow is decreased and renal vascular resistance is increased, probably because of hypotension and decreased cardiac output. Thus other agents may be preferable in patients with renal insufficiency.<sup>81,83,84</sup>

Trimethaphan is given by slow intravenous infusion. Five hundred milligrams are placed in 500 ml of dextrose 5% in water. The infusion rate is initiated at 0.5 to 1.0 mg/min and titrated to obtain the desired blood pressure control. The hypotensive effect is immediate and requires careful bedside monitoring. Once the infusion is stopped a return to pre-infusion arterial blood pressure occurs within minutes. Blood pressure lowering is only evident in the upright position, therefore the head of the bed should be elevated and patients should be in the sitting position. Once satisfactory blood pressure control is achieved, oral therapy should be initiated and the infusion stopped. Prolonged infusion of trimethaphan is occasionally associated with tachyphylaxis due to intravascular volume expansion.<sup>80</sup> Concomitant diuretic therapy potentiates the hypotensive effect and may result in better control of blood pressure.<sup>12,13</sup>

Parasympathetic inhibition by trimethaphan may lead to constipation, paralytic ileus, and urinary retention.<sup>3,79,80</sup> Caution is warranted when the drug is administered for more than 24 hours. Indwelling catheters may be necessary when large doses are given for more than two or three days. Inactivation of pupillary reflexes by trimethaphan may make it difficult to assess the neurologic status of patients with hypertensive encephalopathy or intracranial hemorrhage.<sup>3</sup>

The drug should not be administered to pregnant

women near term because of the danger of producing meconium ileus in the newborn. Trimethaphan should also be avoided in the immediate postoperative period, because it may prolong the duration of bowel and bladder paralysis.<sup>3</sup>

*Methyldopa* (Aldomet<sup>®</sup>) has been used to treat hypertensive crises for a number of years.<sup>1,85,86</sup> At first it was thought that methyldopa decreased norepinephrine synthesis due to decarboxylase inhibition.<sup>87</sup> Subsequently, the false neurotransmitter hypothesis was proposed as a possible explanation for the hypotensive effect.<sup>88</sup> Most evidence favors a central effect of methyldopa, mediated by  $\alpha$ -methylnorepinephrine, a metabolite of methyldopa.<sup>89-91</sup> This metabolite is thought to stimulate central  $\alpha$ -adrenergic receptors and lead to the hypotensive effect. Peripheral release of  $\alpha$ -methylnorepinephrine appears to be of minor importance.

Methyldopa reduces blood pressure by arteriolar relaxation. An orthostatic effect is usually observed, but the difference between supine and erect blood pressure is generally modest.<sup>92</sup> A variable and generally unimportant effect on cardiac output has been observed. Renal vascular resistance is reduced and renal blood flow and glomerular filtration are increased or maintained.<sup>92-95</sup> Cerebral blood flow is also maintained. Plasma renin activity is reduced.<sup>96</sup>

Methyldopa is converted in the body to methyldopamine, methylnorepinephrine and sulfate conjugates. Less than 10% of methyldopa is excreted as methyldopamine and methylnorepinephrine. The remainder is excreted as unchanged methyldopa or its sulfate conjugate.<sup>87</sup> Methyldopa has a biphasic plasma elimination pattern, possibly due to extrarenal elimination of unconjugated methyldopa. The average half-life of the initial phase is 1.7 hours. The half-life increases in patients with renal insufficiency, occasionally resulting in a greater sensitivity to methyldopa.<sup>97</sup>

Methyldopa is generally not a good agent for hypertensive emergencies because of its slow onset of action. A gradual reduction in blood pressure occurs after intravenous administration, with an onset of action usually within three hours, and lasting for 12 hours or more.<sup>3,86</sup> Repeated intravenous administration has been shown to be effective.<sup>85</sup> Methyldopa should be administered in a dosage of 250 to 500 mg diluted in 100 ml of dextrose 5% in water, and infused over 30 minutes. At least three hours should elapse between repeated injections in order to allow the fully hypotensive effect to manifest itself. Orthostatic hypotension may occur and proper precautions should be observed. Oral therapy should be initiated as soon as possible.

The most prominent side effects following methyldopa administration are drowsiness and lethargy, which may interfere with evaluation of neurological status.<sup>3,86</sup> This effect usually disappears after several days of therapy. Decreases in

mental activity,<sup>98</sup> psychosis,<sup>99</sup> mental depression<sup>100</sup> and a parkinsonism-like syndrome<sup>101</sup> have also been reported. Approximately 20% of patients taking methyldopa develop a Coombs'-positive reaction, with less than 1% developing hemolytic anemia.<sup>102</sup> Hepatic injury ranging from mild abnormalities of liver function to fulminant hepatitis, indistinguishable from viral hepatitis, have been observed after methyldopa therapy.<sup>102-105</sup> Drug-induced fever, resembling a flu-like syndrome, has also been reported.<sup>106</sup>

*Reserpine* has been employed successfully in the management of hypertensive emergencies for the past two decades. Reserpine depletes norepinephrine from adrenergic neuron terminals, and prevents uptake of norepinephrine by the neurosecretory chromaffin granules. The net effect is interference with neurotransmission at the postganglionic nerve endings at the interface with vascular smooth muscle.<sup>80,107</sup> The myocardium, adrenal medulla and brain tissues are also depleted of biogenic catecholamines and serotonin.<sup>80,107</sup>

The acute administration of reserpine produces bradycardia and a fall in arterial blood pressure and vascular resistance, but with no consistent effect on cardiac output, renal blood flow or glomerular filtration.<sup>109</sup> Chronic administration may lower cardiac output and prolong atrioventricular conduction time, probably as a result of myocardial catecholamine depletion and a decrease in venous return.<sup>110,111</sup>

Reserpine is administered by the intramuscular route in the treatment of hypertensive emergencies. It may also be administered intravenously, but this has no particular advantage because its onset of action is between two and three hours. A dose of one to five milligrams is administered and may be repeated after four hours. A disadvantage is the potential for drug accumulation and an exaggerated hypotensive response. On the other hand, constant bedside monitoring is not essential. Doses exceeding 8 mg per day are not recommended.<sup>4</sup>

Hypotensive doses of reserpine may cause profound somnolence which is a major deterrent to its use in hypertensive encephalopathy, intracranial hemorrhage and head injuries.<sup>3</sup> Other central nervous system effects include vertigo, weakness, lethargy, headache, nightmares, and depression which sometimes is severe enough to result in suicide.<sup>112-113</sup> These effects are usually seen in higher doses, and appear to be more common after intramuscular administration.<sup>114</sup> Reserpine is also capable of increasing gastrointestinal motility and acid secretion.<sup>115</sup> Bradycardia, prolonged atrioventricular conduction, second degree heart block, and nasal stuffiness may also result.<sup>108</sup> These effects are probably of greater significance with chronic therapy. Hypotensive episodes are generally rare, but patients with cerebrovascular accidents may be sensitized to this effect and should probably be treated with more predictable agents.<sup>116</sup>

*Phentolamine Mesylate* (Regitine®) has been useful in the treatment of hypertensive emergencies associated with an excess of circulating catecholamines, as occurs in pheochromocytoma or during concurrent use of monoamine oxidase inhibitors and sympathomimetic substances.<sup>3,4,117-121</sup> The hypotensive response to phentolamine is mediated by a weak blockade of sympathetic activity and a moderate degree of antagonism to circulating catecholamines, with the greatest effect resulting from a generalized vasodilation of resistance and capacitance vessels of all sizes.<sup>122</sup>

The reduction in peripheral vascular resistance is accompanied by an increase in heart rate and cardiac output, resulting from either an increase or reflex sympathetic tone,<sup>122</sup> a direct central effect,<sup>123</sup> or a direct inotropic effect.<sup>124</sup> A reduction in pulmonary resistance is also noted.<sup>125</sup> Associated with these systemic and pulmonary changes is a marked fall in renal, cutaneous, muscular, and coronary vascular resistance produced by direct dose-dependent relaxation of vascular smooth muscle.<sup>124-126</sup>

Phentolamine is not very effective in hypertensive emergencies, other than during short term use in patients with an elevation of circulating catecholamines. The profound tachycardia and palpitations associated mainly with its parenteral administration and the poor gastrointestinal absorption, profound diarrhea, nausea, and abdominal pain due to gastrointestinal stimulation limit its use.<sup>80</sup>

When phentolamine is used clinically, a dose of 5 mg is injected intravenously or intramuscularly. A hypotensive response usually occurs within 15 to 30 seconds, and lasts for a maximum of only 15 to 30 minutes.<sup>3,122</sup> A constant infusion of 0.2 to 5 mg per minute may also be employed to maintain blood pressure control.<sup>4</sup> Intravenous propranolol may counteract the increase in heart rate associated with the decrease in peripheral vascular resistance.<sup>3</sup>

Phentolamine administration has produced tachycardia, palpitations, arrhythmias and the precipitation of anginal attacks, and must be used with extreme care in susceptible individuals.<sup>3,80</sup>

## SPECIFIC HYPERTENSIVE EMERGENCIES

### *Encephalopathy*

Hypertensive encephalopathy is the most serious complication of accelerated (malignant) hypertension.<sup>18,127</sup> It consists of severe headache, nausea, vomiting, mental confusion, lethargy, nystagmus, visual disturbances, reflex asymmetries, and localized weakness. Arterial pressure often exceeds 250/150 mmHg. Stupor, coma, convulsions and death may occur within hours if the syndrome is not treated.<sup>4,18</sup> Pathological changes include necrotizing arteriolitis, petechial hemorrhages, and multiple small emboli. Cerebral edema, papilledema and elevation of spinal fluid pressure are also common findings.<sup>18</sup> Treatment is aimed at immediate re-

duction in arterial pressure to normotensive levels, which usually results in clearing of the sensorium, cessation of convulsions and reversal of vasoconstriction. Diazoxide, sodium nitroprusside, or trimethaphan camsylate are considered the drugs of choice; reserpine, hydralazine, and methyldopa have the disadvantage of slow onset of action. Furosemide should be used concomitantly in order to maintain urine output and to prevent or reverse retention of salt and water.

### *Accelerated Hypertension*

This clinical syndrome is characterized by severe diastolic hypertension, usually greater than 130 mmHg, and by varying degrees of retinal or renal changes, or both. It may be accompanied by encephalopathy (i.e., visual impairment, headache, nausea, vomiting, neurologic changes) and by rapid deterioration of renal function.<sup>11,128</sup> Many patients tolerate the blood pressure elevation and are not considered hypertensive emergencies. In these individuals, bed rest, diuretic and oral antihypertensive agents are adequate.<sup>11</sup> However, when evidence of brain, heart or renal damage is present, immediate reduction in blood pressure is needed. Diazoxide or sodium nitroprusside are considered drugs of choice for prompt reduction. Reserpine or methyldopa are good alternatives. Again, a diuretic must be coadministered.

### *Hypertensive (Toxemic) Pregnancy*

Fulminant toxemia of pregnancy is characterized by hypertension, edema, proteinuria, headache, visual disturbances, mid-epigastric pain, and seizures.<sup>129,130</sup> Prompt reduction in blood pressure is required to avoid maternal and fetal morbidity. Treatment should include bed rest, salt restriction, diuretics, and possibly sedation. Magnesium sulfate is usually sufficient to control convulsions and lower blood pressure, but parenteral antihypertensives may be needed if this fails.<sup>129</sup> Hydralazine is considered the agent of choice, and most studies support its safety to both mother and fetus. Diazoxide may be used,<sup>131</sup> but inhibition of labor may occur requiring oxytocic therapy.<sup>42</sup> Methyldopa has also been used with some success.<sup>132</sup>

### *Cardiac Decompensation*

When acute left ventricular failure, coronary artery disease or myocardial infarction accompanies an acute elevation in blood pressure, rapid reduction of arterial blood pressure and left ventricular work is effective and usually essential.<sup>4</sup> A hypotensive agent that will not increase cardiac work is desirable. Sodium nitroprusside and trimethaphan are effective because they produce venous pooling and thus do not increase cardiac work. Another advantage of these agents is that a controlled reduction of blood pressure can be achieved by careful adjustment of the infusion rate, thus limiting the risk of hypotension.

## Intracranial Hemorrhage

When a hypertensive episode is complicated by subarachnoid or intracerebral hemorrhage, a prompt reduction of blood pressure sometimes to hypotensive levels may be necessary.<sup>3,4</sup> Sodium nitroprusside or trimethaphan are the agents of choice. A prompt and controlled reduction in blood pressure, without lethargy or somnolence, may be achieved and sustained. If blood pressure reduction produces increasing neurologic disturbances, the infusion can be stopped or slowed down.

## Pheochromocytoma

This catecholamine-secreting adrenal tumor accounts for about 0.5% of cases of hypertension. Symptoms often are paroxysmal, and can include pounding headaches, sweating, palpitations, apprehension, tremulousness, pallor or flushing, nausea, vomiting, abdominal pain, and paresthesias. The blood pressure can exceed 250/150 mmHg, and may lead to myocardial infarction, angina, pulmonary edema, cerebral hemorrhage, and death.<sup>118</sup> Prompt reduction in blood pressure is necessary. Phentolamine is the considered drug of choice both for diagnostic purposes and treatment, but the former use is controversial.<sup>118,122</sup> Because of the tachycardia and cardiac arrhythmias that may result after phentolamine therapy, propranolol should also be initiated.<sup>3</sup> Sodium nitroprusside has also been useful.<sup>133</sup>

## Interactions with Monoamine Oxidase Inhibitors

Occasionally patients taking monoamine oxidase inhibitors develop hypertensive emergencies after ingestion of amphetamines, ephedrine, or tyramine-containing food substances.<sup>119-121</sup> These agents are capable of releasing stored catecholamines resulting in the hypertensive crisis. The treatment is the same as for pheochromocytoma.

## Aortic Dissection

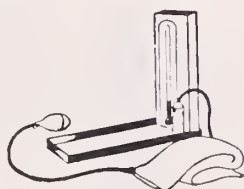
Hypertension associated with aortic dissection requires antihypertensive therapy that does not increase mechanical stress on the aortic wall. Trimethaphan camsylate, sodium nitroprusside, and reserpine are good choices in this situation because they do not increase stroke volume and left ventricular ejection rate.<sup>4,31</sup> Propranolol is also very useful in this situation and is considered the drug of choice by many clinicians.

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### COORDINATED HOME HEALTH CARE EXPANDS

Blue Cross benefits for patient care in the home are now available in York County through an agreement between Blue Cross of Maine and York County Health Services, Inc.

The benefit, called the Coordinated Home Health Care (CHHC) Pilot Program, will be available to patients who are found to be eligible by the program coordinators. Coordinated home care is already available to all Blue Cross subscribers living in Androscoggin, Aroostook, Cumberland, Franklin, and Oxford counties, and now York County has been added to this list of covered areas.

Coordinated Home Health Care is a Pilot Program initiated in 1972, which allows certain patients, who need service, with their doctors' permission, and who live within an area in which Maine Blue Cross has contracted for services, to go home from the hospital early to recuperate, or receive needed services in their home without prior hospitalization.

Under this plan, patients are provided services through a home health agency under a physician's plan of treatment, designed specifically to provide the medical and nursing care so vital to recovery.

This unique program was inaugurated for many reasons. Major among them was the patient who is more comfortable recuperating in the familiar and friendly surroundings of his own home. In enabling a patient to receive the services he needs at home, it frees up an acute care bed in the hospital.

A subscriber eligible for Coordinated Home Health Care is covered for such benefits as: "Visits" from the attending physician; a registered or licensed practical nurse; a registered speech, occupational, dietary or physical therapist; and home health aides. A "visit" is any service prescribed by the attending physician. Three "visits" are allowed for every unused benefit day under the patient's Blue Cross contract. "Prescribed drugs, appliances, dressings, supplies, and tests" are furnished without limitations while the patient is under Coordinated Home Health Care. "Transportation by ambulance" is provided when prescribed by a physician. Each use of transportation is considered a "visit."

The patient and his or her family must also agree that they wish to use the Coordinated Home Health Care Program.

To assure that the new home care program is used to its fullest potential, frequent review meetings will be held by the participating staff members to discuss patient progress. The agency's coordinator will participate in the discharge planning process in each of the local hospitals to help identify appropriate candidates early.

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**INDICATIONS:** Therapeutically (as an adjunct to systemic therapy when indicated) for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

**Prophylactically,** the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing. **CONTRAINDICATIONS:** Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

**WARNING:** Because of the potential hazard of nephrotoxicity and ototoxicity due to



neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended. **PRECAUTIONS:** As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. **ADVERSE REACTIONS:** Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML



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# News, Notes and Announcements

## State of Maine Department of Human Services Division of Child Health Clinic Schedule — 1977 By Appointment Only

### Orthopedic Clinics

Bangor — St. Joseph Hospital  
9:00 a.m.: Jan. 27, Feb. 24, Mar. 24, Apr. 28, May 26, June 23,  
July 28, Aug. 25, Sept. 22, Oct. 27, Nov. 17, Dec. 22  
Fort Kent — Northern Maine Medical Center  
9:00 a.m.: Mar. 15, May 10, July 12, Sept. 13, Nov. 15  
Houlton — Houlton Regional Hospital  
10:00 a.m.: Mar. 14, May 9, July 11, Sept. 12, Nov. 14  
Lewiston — Central Maine Medical Center  
Orth., 9:00 a.m.: Feb. 18, Apr. 15, June 17, Aug. 19, Oct. 21,  
Dec. 16  
Scol., 9:00 a.m.: Jan. 21, Feb. 18, Mar. 18, Apr. 15, May 20,  
June 17, July 15, Aug. 19, Sept. 16, Oct. 21, Nov. 18, Dec. 16  
Presque Isle — A. R. Gould Memorial Hospital  
9:00 a.m.: Mar. 16, May 11, July 13, Sept. 14, Nov. 16  
Waterville — Mid-Maine Medical Center (Thayer Unit)  
(Time scheduled by hospital): Feb. 7, Mar. 7, Apr. 4, May 2,  
June 6, Sept. 12, Oct. 3, Nov. 7, Dec. 5

### Cleft Palate Clinic

Portland — Maine Medical Center  
9:00 a.m.: Feb. 14, May 16, Sept. 19, Nov. 21

### Cardiac Clinics

Bangor — St. Joseph Hospital  
9:00 a.m.: Feb. 11, Mar. 11, Apr. 8, May 13, June 10, July 8,  
Aug. 12, Sept. 9, Oct. 14, Nov. 18, Dec. 9

Portland — Maine Medical Center

9:00 a.m.: Jan. 21, 18, Feb. 4, 11, 25, Mar. 4, 11, 18, 25, Apr. 1,  
15, 22, 29, May 6, 13, 20, June 3, 10, 17, 24, July 8, 15, 22, 29,  
Aug. 5, 12, 19, 26, Sept. 9, 16, 23, 30, Oct. 7, 14, 21, 28, Nov.  
4, 18, Dec. 2, 9, 16, 30

### Children's Development Clinics

Lewiston — Central Maine Medical Center  
8:30 a.m.: Feb. 28, Mar. 14, Apr. 11, May 9, June 13, July 11,  
Aug. 8, Sept. 12, Oct. 24, Nov. 14, Dec. 12  
Waterville — Mid-Maine Medical Center (Thayer Unit)  
8:30 a.m.: Feb. 16, Mar. 2, Apr. 6, May 18, June 1, 15, 29, July  
6, 20, Aug. 3, 17, Sept. 7, Oct. 5, 19, Nov. 2, 16, Dec. 7, 21

### Cystic Fibrosis Clinics

Lewiston — Central Maine Medical Center  
(Time scheduled by hospital): Feb. 4, Mar. 4, Apr. 1, May 6,  
June 3, July 1, Aug. 5, Sept. 2, Oct. 7, Nov. 4, Dec. 2  
Portland — Maine Medical Center  
(Time scheduled by hospital): Jan. 18, Feb. 15, Mar. 15, Apr.  
19, May 17, June 21, July 19, Aug. 16, Sept. 20, Oct. 18, Nov.  
15, Dec. 20  
Bangor — St. Joseph Hospital  
(Time scheduled by hospital): Jan. 18, Feb. 15, Mar. 15, Apr.  
19, May 17, June 21, July 19, Aug. 16, Sept. 20, Oct. 18, Nov.  
15, Dec. 20

## Rational Use of Antibiotics

Colby Weekend College — Postgraduate Medical Education  
Sponsored With the Maine Medical Association and the Mid-Maine Medical Center  
March 5 and 6, 1977, Colby College, Waterville, Maine

### Saturday, March 5

10:00-10:30 A.M.  
Diagnosis of Infection — Role of Gram Stain and Culture  
Robert Wise, M.D., Togus, Maine  
10:30-11:00 A.M.  
Effective New Antibiotics  
Thomas Claffey, M.D., Portland, Maine  
11:00-12:00 M.  
Workshop  
12:00 M.-1:00 P.M.  
Lunch  
1:00-1:30 P.M.  
Upper Respiratory Tract Infections  
David R. Ginder, M.D., Waterville, Maine  
1:30-2:00 P.M.  
Community Acquired Pneumonias  
GUEST SPEAKER: Arnold Weinberg, M.D., Professor of  
Medicine, Harvard  
2:00-3:00 P.M.  
Workshop  
3:00-3:30 P.M.  
Recess  
3:30-4:00 P.M.  
Infectious Diarrhea  
William Hall, M.D., Portland, Maine  
4:00- 4:30 P.M.

Hepatitis  
William Nersesian, M.D., Augusta, Maine  
4:30-5:30 P.M.  
Workshop  
6:00-7:00 P.M.  
Cocktails  
7:00-8:00 P.M.  
Dinner  
8:00-9:00 P.M.  
Gynecologic Infections  
GUEST SPEAKER: Arnold Weinberg, M.D., Professor of  
Medicine, Harvard

### Sunday, March 6

9:00-9:30 A.M.  
Urinary Tract Infection  
Bruce Denny-Brown, M.D., Bangor, Maine  
9:30-10:00 A.M.  
Gonorrhea  
Peter Leadley, M.D., Waterville, Maine  
10:00-11:00 A.M.  
Workshop  
11:00-12:00 M.  
Nosocomial Infection  
Michael Bach, M.D., Lewiston, Maine  
12:00 M.-1:00 P.M.  
Workshop

Fee: \$85.00 (Includes course fee and Saturday lunch, reception and banquet). Minimum Enrollment: 30; Maximum Enrollment: 60.  
For further information write to: Robert Kany, Colby College, Waterville, Maine 04901.

# County Society Notes

## Penobscot

The monthly meeting of the Penobscot County Medical Society was held on October 19, 1976 at the Heritage Motor Inn in Millinocket, Maine.

The meeting was opened by the President, Dr. John A. Woodcock and the minutes of the previous meeting were read and approved.

Under old business, the slate of nominees for the 1977 County Delegates and Alternates were presented by Dr. David M. Senenig, Chairman of the Nominating Committee. This includes the following:

Delegates: Drs. Robert P. Andrews, Francis I. Kittredge, Carroll P. Osgood, Jr., Leonardo L. Leonidas, Jack N. Meltzer and David S. Beebe, all of Bangor; and John J. Pearson, Old Town. Alternates: Drs. James R. Curtis, Sidney Chason, G. Douglas Timms, Parker F. Harris, John F. Adams, Jr., Don L. Maunz and Allison K. Hill, all of Bangor.

This slate was unanimously approved by the membership.

The question whether to participate in the Diabetes Detection Program of the Maine Medical Association was again considered. Correspondence from Dr. Melvin Bacon urging us to participate was read. Our past experience in the program was summarized by Dr. Philip G. Hunter. It was again the overwhelming consensus of opinion by the membership that the effort involved in the program far outweighed the yield and, as in the past two years, the County Society does not wish to participate.

Applications for membership in the County Medical Society were presented. Drs. John R. Mootz and Paul A. Shapero were unanimously approved for full membership in the Society and Drs. Donald E. Stillwagon, Christopher R. Brigham, Harold E. Lutz, Jeffrey F. Hankoff and Peter J. Laursen were unanimously approved for junior membership in the Society.

Dr. Pearson raised the question of county physician participation in the swine flu program. He felt there was too little physician input. Dr. Pearson also expressed his concern regarding the possible closing of the Bangor Mental Health Institute.

A motion was made by Dr. Bourcard Nesin and amended by Dr. Walter L. H. Hall that the County Society should go on record with the State authorities that it favors retaining Bangor

Mental Health Institute and would strongly support further investigation into the feasibility of upgrading its services. The motion unanimously passed and action will be taken by the executive committee.

In regards to the swine flu vaccine program, Dr. Robert P. Andrews also expressed his concern over the lack of physician coverage. It was noted by Dr. Pearson that the family practitioners had made some attempt to get involved this past summer, but as of this time, they feel they are not adequately participating due to lack of interest in the State authorities to include them.

Following the business meeting, Dr. Henry Ryan, the Chief Medical Examiner for the State of Maine, presented an enlightening talk and slide show. The important role the medical examiner plays in local medicine was emphasized. The problems and pitfalls that one may encounter in arriving at a cause of death were elucidated.

The meeting was then adjourned.

H. CLEMENT JURGELEIT, M.D., *Secretary*

## Kennebec

A meeting of the Kennebec County Medical Association was held at the Silent Woman in Waterville, Maine on October 21, 1976.

The meeting was called to order at 8:11 p.m. by the President, Dr. James C. Hayes, with 31 members and one guest in attendance.

Correspondence was read. The second reading of the applications of Drs. Anton Braun, Stephen H. Eccher, Daniel B. Clarke and Henry F. Ryan were read and the Society voted to accept them into membership.

Dr. Richard T. Chamberlin discussed with the Society the activities of the Executive Committee in regard to the malpractice question. This is obviously a matter of considerable interest to the members of the Society and finally, Dr. Hayes introduced Dr. Henry Ryan who presented a very interesting discussion of forensic medicine.

O. THOMAS FEAGIN, M.D., *Secretary*

# Letters to the Editor

To the Editor:

The subject of diethylstilbestrol (DES) exposure *in utero* is a familiar one to members of the Maine Medical Association. You may know that the National Cancer Institute's Division of Cancer Control and Rehabilitation is directing a study in four institutions, called the DESAD project, of DES-associated vaginal and cervical irregularities and the rare instances of clear-cell adenocarcinoma that occur in DES-exposed daughters.

The text of the *Information for Physicians - DES Exposure In Utero* pamphlet was compiled by the physicians of the DESAD Project's Professional and Public Relations Subcommittee, and edited by the Office of Cancer Communications of the National Cancer Institute.

This information is very important to every physician in this country who is at all likely to be contacted concerning DES exposure *in utero*.

The pamphlet answers questions physicians and patients are now asking. The DES-type drugs that may have been prescribed to pregnant women are listed. A bibliography is included. Among the questions are:

- What is diethylstilbestrol (DES)?
- Why were DES-type drugs used in pregnancy?
- What is the cancer problem associated with *in utero* exposure?

- What noncancerous irregularities occur with this exposure?
- If the patient was exposed to DES-type drugs, what should be done?
- What about follow-up examinations?
- What is the management of vaginal and cervical irregularities other than clear-cell adenocarcinoma?
- Where do the cancers that have been diagnosed occur?
- What is the therapy for these cancers?

This *Information for Physicians* pamphlet is available at no cost from the National Cancer Institute's Office of Cancer Communications, Bethesda, Maryland 20014.

Two other publications on this subject also are available without charge — *Questions and Answers About DES Exposure Before Birth* and *Were YOU or YOUR DAUGHTER Born After 1940?*

Thank you very much for your cooperation.

FRANK J. RAUSCHER, JR., Ph.D.  
Director, National Cancer Program

To the Editor:

I read the article on plaster casts for Colles' fractures in the August issue of the *Journal of the Maine Medical Association* the other day and thought it might be worthwhile to comment on the article.



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Although the idea of indenting the cast as he pointed out to prevent slipping of the fracture makes sense and is frequently done by all of us, I would prefer to indent the radial side of the wrist. He states that ulnar deviation is avoided because it causes ulnar tilting of the articular surface of the radius. It is my opinion that the articular surface of the radius has a normal ulnar tilt and the object of treatment is to reduce that tilt and maintain it. In order to do this, one has to mold the cast not only at the radius but usually at the radiocarpal and metacarpal joints. I noticed from the cast that the thumb is completely cut out which would allow the hand to come back into radial deviation and would allow the radius to shorten. The only other point I would make is that the cast seems to extend beyond the MP joints. This is fine in young people but if the MP joints aren't kept free in elderly women who usually get Colles' fractures, they are apt to get stiffness which may be permanent in the MP joints.

LAWRENCE CRANE, M.D.  
157 Pine Street  
Portland, Maine 04102

#### To the Editor:

The paper by True, et al — "Health Planning for Primary Care in Rural Shortage Areas," *Journal of the Maine Medical Association*, Vol. 67, November 1976, is a welcome addition to our understanding of primary physician manpower coverage in the State of Maine.

I am curious that the authors made no mention of the present and future contribution that nurse practitioners and physician assistants can make in providing rural health care.

In the fourth paragraph, page 331, the article contains a quote of a 1975 report to the Maine Planning Office, "Maine's death rates were higher than the U.S. figure because of our relatively large elderly population and lack of an efficient medical care system" (emphasis mine). Do the authors really believe that a

sizeable influx of primary care physicians is going to achieve a significant lowering of mortality rates in rural Maine? Doctoring, in my opinion, makes very little impact upon morbidity or mortality rates. The rationale for more primary care physicians in rural Maine should rest on other considerations: primarily improved access to medical care.

GEORGE T. NILSON, M.P.H.  
Executive Director  
Maine Lung Association  
20 Willow Street  
Augusta, Maine 04330

#### To the Editor:

The article, "Health Planning for Primary Care in Rural Shortage Areas" by Drs. True, Caven and Frechette, (J.M.M.A. 67: 326, Nov., 1976) purports to be "an in depth study of Maine primary care physicians . . .". The authors present numerous data to support their conclusion that, to meet the present requirements of Maine, "357 more primary care physicians" are needed.

Although I do not dispute their general thesis, I would have greater confidence in their statistics if the authors had not apparently overlooked one significant factor: namely, the osteopathic physicians in Maine, many of whom serve as primary physicians. Nowhere in their article did I see any indication that this rather significant source of medical manpower was included in the statistical considerations of physician-population ratios.

Possibly I am mistaken. I hope I am. Indeed, I trust that the conclusions and recommendations of this study were not reached in an allopathic vacuum. To do so would be unrealistic and misleading.

KEVIN HILL, M.D.  
325A Kennedy Memorial Drive  
Waterville, Maine 04901

Reply:

Doctor Kevin Hill's criticism of our article "Health Planning for Primary Care in Rural Shortage Areas," is a valid one deserving some explanation.

There is little doubt that Maine's osteopathic primary care physicians render a great service to the people of the State. Furthermore, it should be added that the great majority of the State's practicing doctors of osteopathy are generalists.

When we initiated our study in 1975, we were attempting to do a comparative study of general internists, pediatric generalists, and family physicians. The ranks of family physicians are swelled by the addition of osteopathic generalists but only a few osteopathic physicians are categorized as internists or pediatricians.

When we began our study in 1975, we noted that in 10 of 16 Maine counties, less than 10% of the physicians were osteopaths. Despite this fact, Doctor Hill's criticism is appropriate and the statement that only 55% of the primary care needs are being met in Maine should be modified although there is little doubt in my mind that there is a significant shortage of both allopathic and osteopathic primary care providers.

ROBERT M. TRUE, M.D.  
ROBERT E. CAVEN, M.D.  
RICHARD P. FRECHETTE  
Maine Medical Center  
Portland, Maine 04102

To the Editor:

An interesting case has been reported by M. A. LaCombe in the November issue of the *Journal of the Maine Medical Association* (67: 334, 1976) as "Gynecomastia in Neurofibromatosis." I wish to dispute that diagnosis on clinical grounds. The excellent photographs reveal a unilateral systematized nevus localized to the right shoulder girdle and upper trunk in association with obvious right sided gynecomastia (or possibly pseudogynecomastia). In addition to areas of macular hyperpigmentation, this giant nevus is composed of areas of hypertrichosis and still other areas of verrucous epidermal changes. Certainly hyper-

trichosis and verrucous epidermal changes are not characteristic of cafe-au-lait spots. Furthermore, there is no mention of axillary freckling (Crowe's sign) actually being present. Finally there is a notable absence of cutaneous neurofibromas invariably present in patients 40 years of age.

The cutaneous findings in this case are those of a systematized epidermal nevus (epidermal nevus syndrome). Macular hyperpigmentation, angiomas, hypertrichosis and other hamartomatous growths in addition to skeletal, soft tissue and neurologic defects are common findings in such cases (Solomon, L. M., et al, "The Epidermal Nevus Syndrome," *Arch Derm* 97: 273, 1968.)

Stein recently reported (Stein, K. M., et al, "Neurofibromatosis Presenting as the Epidermal Nevus Syndrome," *Arch Derm* 105: 229, 1972) the case of a 13-year-old boy who had the combined findings of both the Epidermal Nevus Syndrome and Pretumorous Neurofibromatosis. However, their case had multiple cafe-au-lait spots, axillary freckling and a petrous ridge neurofibroma in addition to systematized epidermal nevus.

Histologic examination of appropriate specimens would be of interest and of help. Examination of routine H&C section would reveal the true nature of the breast tissue and would also confirm the presence of an epidermal nevus. Examination of Dopa stained sections would reveal the presence or absence of giant melanosomes diagnostic of neurofibromatosis (Benedict, P. H., et al, *JAMA* 205: 618, 1968).

I suspect they would not be present. Is this the first reported case of gynecomastia (or pseudogynecomastia) associated with a Systematized Epidermal Nevus?

THOMAS L. WATT, M.D.  
Dermatology Section  
Eastern Maine Medical Center  
Bangor, Maine 04401

Reply:

I commend Dr. Watt on his clinical acumen. Based on the photographs as presented in the case report, he has every reason to question the diagnosis of neurofibromatosis. From the vantage



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point of an internist, my interest in the case stemmed from differentiating between Albright's syndrome and von Recklinghausen's neurofibromatosis, both in an historical sense and in the clinical presentation of this patient. From a dermatologist's vantage point, the differential diagnosis might well include epidermal nevus.

There are several points in Dr. Watt's letter which I think require clarification and amplification. The photographs in the paper reveal a macular hyperpigmented skin lesion with superimposed, nodular, verrucous, plexiform changes. Whether this is neurofibromatosis or epidermal nevus remains to be decided by the pathologist. The skin lesion in question did not exhibit hypertrichosis. The patient did not have Crowe's sign, i.e., axillary freckling, which, when it occurs, is certainly strong evidence of neurofibromatosis, but actually only occurs in about twenty percent of patients with von Recklinghausen's disease. Contrary to Dr. Watt's statement, cutaneous neurofibromata are not uncommon to patients of this age having neurofibromatosis.<sup>1</sup>

In considering the differential diagnosis of epidermal nevus syndrome versus von Recklinghausen's neurofibromatosis, one exciting aspect involves the possibility that epidermal nevi may be inherited as an autosomal dominant defect with low penetrance. Thus, in addition to skeletal, soft tissue and neurological defects, the two diseases possibly have in common a similar mode of inheritance. The common denominator in Solomon's twelve cases of epidermal nevus syndrome was the finding of hyperkeratosis on pathological examination, with four of the cases exhibiting epidermolysis (vacuolization of the granular layer of the epidermis) as well.<sup>2</sup> With regard to Dr. Watt's suggestion that pathological examination include a search for giant melanosomes, Stein's paper makes the point that this is useful and necessary only in the pretumorous stage of neurofibromatosis, in which case a melanotic macule should contain these giant melanosomes.<sup>3</sup>

The accompanying photomicrographs give us the answer. The skin biopsy was taken from the medial border of the verrucous, plexiform skin lesion on the right breast (see Figure 3 in the original article). At my request the pathological specimens were reviewed by Dr. Stanley M. Becker and by his Department of Pathology at Monmouth Medical Center, Long Branch, New Jersey. The slides were reviewed as well by Dr. Harbans Sodhi, of Stephens Memorial Hospital, Norway, Maine, who kindly supplied the accompanying photomicrographs. All pathologists agree that this skin lesion is neurofibromatosis, that there is no hyperkeratosis, hypertrichosis, angiomas, or other epidermal

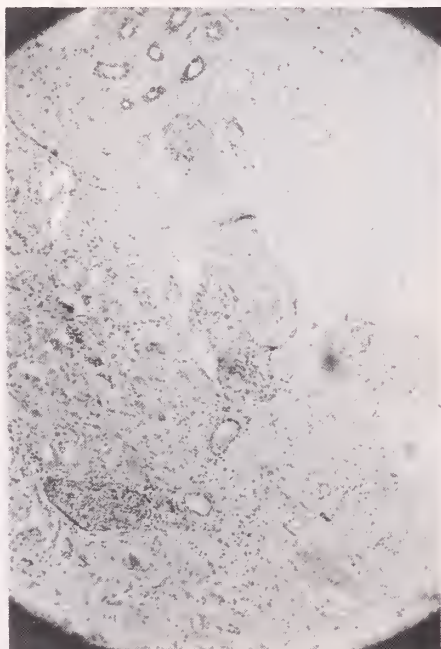


Fig. 1. Low power view of neurofibromatous lesion. 1x100

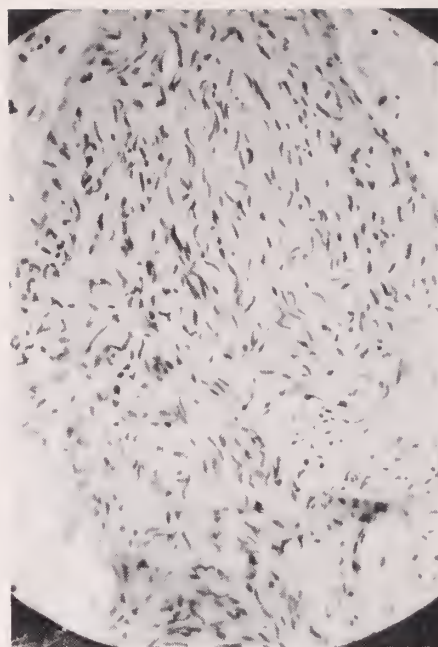


Fig. 2. Nerve bundle with surrounding neurofibroma. 1x400

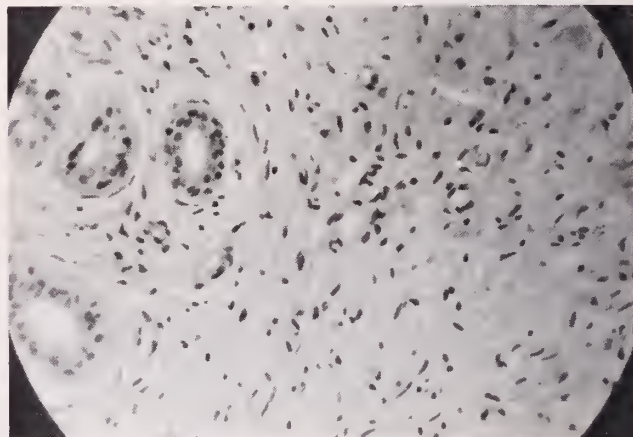


Fig. 3. Neurofibroma surrounding sweat glands. 1x400

change causing this skin lesion. Since the patient would not submit to a breast biopsy, one cannot answer the question of whether he had gynecomastia or "pseudogynecomastia". That is to say, pathologically we cannot determine whether the patient's breast enlargement was secondary to mammary tissue (gynecomastia) or secondary to an underlying lipoma (pseudogynecomastia), the latter of which possibilities I had suggested in the original article. In summary then, this is the first case of nonhormonal-induced gynecomastia in von Recklinghausen's disease.

I thank Dr. Watts very much for his letter and for his interest in this case.

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## Multiple Small Bowel Diverticula

### A Review and Case Presenting With Both Malabsorption and Acute Hemorrhage

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While a few small bowel diverticula are commonly seen on routine UGI radiographs and are of questionable significance, it is rare to have more than a dozen readily identifiable in the absence of scleroderma. This paper records a patient with long-standing symptoms which were compatible with malabsorption syndrome and who presented with an acute GI hemorrhage and in whom at least two dozen easily counted jejunal and ileal diverticula are seen on a small bowel series.

#### CASE REPORT

Patient R.G., a 74-year-old man, was admitted to Central Maine Medical Center on October 4, 1975 with brisk bleeding of dark blood with clots into his transverse colostomy bag which had been placed in 1968 because of a perforated sigmoid diverticulum. Second and third stages of the colonic diverticular surgery were postponed however because the patient developed mild, non-specific proctitis and sigmoiditis after the original surgery. Cultures have been negative for pathogens and the appearance and the biopsy did not clearly demonstrate either ulcerative or granulomatous colitis. He intermittently passed mucus mixed with a small amount of blood per rectum over the years, but more troublesome was the extremely malodorous colostomy drainage without blood until his admission in October, 1975. He had had trouble maintaining his weight and would get flatulent and "gassy" on a regular diet. He had found by trial and error that fatty foods exacerbated his symptoms.

In his previous workups, barium enemas had revealed no right-sided colonic diverticula, and previous upper GI's were only followed to the third and fourth portions of the duodenum where two diverticula were noted.

Upon admission in October, 1975 he had tachycardia and mild hypotension. After stabilization a Hypaque® enema and later a barium enema revealed no neoplasm, ulceration, or diverticulum in the right colon. No blood came from the left colon at the site of the double-barreled transverse colostomy or from the by-passed rectum; esophagogastroduodenoscopy was performed and showed no lesion or any blood to the second portion of the

duodenum. As the colonic mucosa, as seen through the colostomy, was grossly normal it was assumed that the GI bleeding must be coming from the intervening bowel, i.e., between the second duodenal portion to the ileocecal valve. Thus, a small bowel study was performed revealing the innumerable diverticula (see Fig. 1 and 2). There was no overt malabsorption pattern. Bleeding spontaneously ceased after the barium studies although three units of whole blood had been required.

Pertinent laboratory studies revealed a strongly positive urinary indican, normal prothrombin time and other bleeding indices, low serum carotene (40 micrograms/deciliter with normal over 100 micrograms/deciliter), normal folic acid of 13.3 nanograms/milliliter and normal vitamin B12 levels of 375 picograms/milliliter. SMA screen was otherwise essentially normal. Hemoglobin and hematocrit the previous June of 1975 had been normal.

The patient received a course of tetracycline therapy (250mg b.i.d. for one week) after which repeat serum carotene rose to 105 micrograms/deciliter, but after discontinuing tetracycline for one week the carotene fell again to 55 micrograms/deciliter. Fecal fat excretion was not measured for technical reasons but would have been an even more sensitive marker for malabsorption than the serum carotene. D-xylose tolerance test (25 gm.) was 4.2 grams in 5 hours, a normal value; the latter being done while the patient was on antibiotic therapy. On therapy the patient symptomatically improved with decreased flatulence and improved stool odor and consistency. The patient was not achlorhydric — Histalog gastric analysis revealed a basal acid output of 0.6 mEq/hour and a peak acid output of 24.3 mEq/hour. A prolonged trial (four months) of salicylazosulfapyridine, 1 gm. t.i.d., seemed to have no beneficial effect when given in addition to the dose of tetracycline given above. Stools had been negative for ova and parasites.

#### DISCUSSION

Although the colon is the most common site for diverticulosis in the intestine in general and the duodenum the most common site in the small intestine, this discussion will be restricted for brevity to out-pouching of the jejunum and ileum as manifested by the presented case. Small bowel diverticula are generally "false" in that they contain only mucosa and submucosa and not muscle layers. They

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Fig. 1. Two and one-half hour film showing ileal diverticula quite well.

almost invariably occur on the mesenteric border of the gut as opposed to Meckel's diverticula. Possible mechanisms include the very likely but unproved theory that pulsion herniations of mucosa occur at weak points of blood vessel penetration into the gut. This theory has been applied to colonic diverticula as well. Whether the pathogenesis involves defective or insufficient collagen or connective tissue, or a defect in smooth muscle itself is not known. Also not known is why diverticula are inconstant through the gut — existing in the colon and duodenum but sparing the jejunum in some patients, but as in the presented case sparing the entire right colon but widely affecting the jejunum and ileum. If higher pressures and firmer fecal contents were important pathogenetically, one would expect the right colon and ileum to be more predisposed than the jejunum. Perhaps there is greater anatomic strength or elasticity in the ileal mucosa with its greater active transport and "tight junctions," however there are no data on the subject.

With regard to the jejunum, an occasional diverticulum found incidentally on upper GI series is not rare and probably of no great clinical or prognostic significance; but multiple pouches are rare and may

be associated with medical and surgical problems. How many diverticula in the small bowel are too many? Or to state the question another way, what is the allowable natural incidence in the aging gut? The answer is not known but at least it is probable that multiple diverticula are an acquired defect because 80-90% of those patients so affected are over 40 years old. Also, it is not known how many pouches are required to produce the symptoms which bring the patient to the physician.

Clinical features are expectedly variable ranging from "chronic indigestion, flatulence, and anorexia to urgency to stool and diarrhea," the latter often malodorous. Malabsorption of fat has been shown in several patients and has been termed a variation of the "blind loop syndrome" which is in fact a diverse entity. In the absence of conditions which predispose to bacterial colonization of the upper gut, i.e., scleroderma, massive intestinal resection or ileocecal valve resection, diabetic enteropathy, acquired immuno deficiency states, or the original afferent loop syndrome, then jejunal diverticula are the most important predisposing cause of bacterial-induced malabsorption. Bacterial counts ranging from  $10^8$  to  $10^{10}$ /cc. of a fecal type may be seen in the upper gut which is normally sterile or nearly so. Bacterial enzymes deconjugate bile salts thereby creating micelle deficiency leading to fat maldigestion. Hydroxylated fatty acids produced by other enzymes may be diarrheogenic themselves. Overgrowth of bacteria may lead to a competition for vitamin B12 and a host deficiency of that substance. Calcium and fat-soluble vitamins may also be lost if the patient continues to eat fatty foods which are malabsorbed and carry vitamins with them.

The other major presentation of small bowel diverticula is acute hemorrhage manifested by melena or dark blood per rectum and the usual changes in vital signs if the bleed is severe. This may be the first and most serious sign of the condition. According to Taylor who reported 35 cases in 30 series through 1969, the mortality of bleeding small bowel diverticula was 20% with good medical and surgical management. Bleeding however may not be acute but may occur chronically in about a quarter of the patients upon reviewing the findings of several authors. Proving the site of bleeding has been markedly simplified with the recent advent of flexible endoscopic instrumentation both for the stomach and for the colon. Colonoscopy of course is often impossible in an acute situation and even arteriography requires very brisk bleeding, usually over 1/2 cc/minute, to show a definite site of origin. Even experienced surgeons may find exact location of bleeding difficult at operation. Other surgical complications include actual diverticulitis with pain and perforation and even enterolith ileus has been reported.

#### COMMENT

The case presented here is both typical and atypical.



Fig. 2. Late film (24 hr.) showing retained barium in jejunal and ileal diverticula.

cal. The patient was typically male and elderly. The literature reports the male to female ratio somewhere between 2:1 to 3:2. He was atypical in that he had both acute (bleeding) and chronic (malabsorptive) manifestations of jejunal, ileal, and duodenal diverticula. The source of bleeding was not definitely proved by surgery which the patient did not require but one can assume a high probability of hemorrhage from the small intestine based on a negative upper GI endoscopy and the presence of a transverse colostomy with a negative right colon and no blood coming from the distal loop. The improvement in symptoms in carotene levels correlated well with the administration of tetracycline in relatively low doses. Discontinuation of the antibiotics caused return of the malabsorptive symptomatology although no further bleeding occurred. It has been tempting to theorize that decreasing bacterial colonization and possibly local inflamma-

tion in a diverticulum had helped to thwart further bleeding but there is no scientific evidence to support this theory and there is probably no relation between an overstretched nutrient vessel which spontaneously ruptures and bacterial colonization contained within intact mucosa.

Although multiple or even massive small bowel diverticulosis is rare, the diagnosis should be considered in a patient with obscure bleeding or malabsorption and the importance of obtaining a small bowel x-ray study is apparent.

#### ACKNOWLEDGEMENT

Waldo Clapp, M.D., Lewiston, Maine, for referring the patient for the study.

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*Continued on Page 98*

# Solitary Non-Parasitic Cyst of the Liver

## Case Report

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BEHZAD FAKHERY, M.D.\*\* and RUDOLPH HAAS, M.D.†

Solitary non-parasitic cysts of the liver are relatively rare. So far only approximately 350 cases have been reported in the literature. In a recent series from the Cleveland Clinic Foundation, 10 cases of cyst of the liver were found between 1961 and 1972, and of these only 3 were single cysts — the others being multiple and associated with polycystic disease of the kidney. The Lahey Clinic Foundation reported 18 solitary unilocular cysts of the liver from 1950 to 1970. Nine patients with this entity were seen at U.C.L.A. and Woodworth Veterans Hospital between 1956 and 1971.

Recently, we had the occasion to observe one case of solitary non-parasitic cyst of the liver at the Central Maine Medical Center, that we wish to report here.

## CASE HISTORY

The patient is a 63-year-old male who in the course of an annual exam in October 1975 was noted to have slight hepatomegaly approximately one finger below the costal margin. The patient, at that time, was entirely asymptomatic. He was seen in July 1976 for management and evaluation of his hypertension at which time he was noted to have a painless mass in the right upper quadrant area attached to the liver. There has been no weight loss, chills, fever, jaundice or anorexia. Past history consists of inguinal hernia repair, mild diabetes controlled by diet, and mild hypertension which was treated with Metahydrin®. A review of systems was essentially unremarkable. Examination revealed a well developed and nourished middle age male appearing to be younger than his stated age. Blood pressure 170/90, pulse 80, temperature 37. There was a 12 x 12 cm. painless smooth rounded mass over the right upper quadrant area beneath the lower costal margin. Laboratory data: Patient profile, CBC, urine are entirely normal. The alpha feto protein before surgery was 37 mcg. (normal 3-15 mcg.). This is in contrast with high levels reported for hepatomas (20,000-30,000). Sigmoidoscopy was negative to 20 cm., Barium Enema showed depression of the right half of the transverse colon by an enlarged liver mass. The upper GI series was also normal. An Intravenous Cholangiogram (Fig. 1) shows normal appearing hepatic radicles, hepatic and common ducts. There is an extrinsic pressure defect of the superior aspect of the gallbladder. The liver scan (Fig. 2) visualized a large filling defect in the area of the porta hepatis. The ultrasonogram (Figs. 3 and 4) confirmed the cystic nature of this mass which is ultrasonographically within the liver. A laparotomy was done through a right upper paramedian incision and a unilocular subcapsular cystic structure was noted in the undersurface of the medial segment of the left lobe of the liver which contained approximately 800 cc. of clear fluid. The wall of the cyst was quite thin. No apparent communication with the biliary duct system nor with any major systemic or portal blood vessel was noted. The

mass was easily shelled out even though it was quite adherent to the liver parenchyma in the region of the undersurface of the liver. Sections of the cyst wall show an inner lining composed of a monolayer of uniform appearing, flattened cuboidal cells. Portions of the inner lining are eroded. The wall is irregularly fibrotic, and attached to the outer surface is atrophic liver parenchyma together with proliferating, dilated bile ducts. The patient had an uneventful post surgical recovery and was discharged on the 8th postoperative day.

## DISCUSSION

Cysts of the liver may have different etiologies and classifications. A distinction should be initially made between a solitary cyst of the liver and polycystic disease of the liver, which most likely is associated with polycystic disease of the kidneys and other organs. Solitary cyst of the liver, on the other hand, may have multiple etiologies, including parasitic, traumatic, inflammatory, congenital or neoplastic either benign or malignant. Table 1 is a classification of non-parasitic cyst of the liver, based on their presumed etiology, proposed by Hansen, et al (1956).

TABLE 1

- A — Congenital
  - 1 — Solitary — unilocal
  - Multilocal
  - 2 — Diffuse polycystic disease
- B — Traumatic
- C — Inflammatory
  - 1 — Specific
  - 2 — Non-specific
- D — Neoplastic
  - 1 — Benign
  - 2 — Malignant

The case we are reporting here, from the histologic point of view, is probably classified in the category of congenital unilocular solitary cyst. Moschovitz in 1956 reported the actually prevalent theory of the origin of the solitary unilocular or multilocular variety as developing from aberrant bile ducts with subsequent inflammatory hyperplasia and obstruction. This theory is supported by the presence of cuboidal epithelium lining the cyst wall.

Solitary congenital cysts have been found at all age groups but more commonly in the 5th and 6th decades. However, patients a few days old or in their seventh decade have been found. A predominance of female in the ratio of 4 to 1 has been generally reported, although in the U.C.L.A. series there were 5 males and 4 females.

One of the characteristic clinical features of this

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Fig. 1. I.V. Cholangiogram. Extrinsic pressure defect of the superior aspect of the gallbladder.

entity is usually a lack of specific symptoms. The patient may notice a fullness in his abdomen or a non-tender mass is incidentally found on a physical exam, as in the case of our patient. Indeed, many cysts of the liver were an incidental autopsy discovery. There is no nausea, vomiting, anorexia or jaundice or fever, but in some cases, due to their large size, cysts have produced compression symptoms of adjacent organs.

The liver tests are usually normal but when associated liver disease is present the biochemical study of the liver may be found to be abnormal.

On physical exam hepatomegaly is invariably found, without tenderness or jaundice.

Standard roentgenographic studies are usually of little help, showing mainly the effect of a right upper quadrant mass or hepatomegaly with displacement of the adjacent organs as can be demonstrated on a barium enema, upper GI series or gallbladder study. For this latter the IV cholangiogram has the advantages of visualizing the extra-hepatic ducts and therefore ruling out the possibility of a choledochal cyst, although this latter has a more specific clinical presentation. The IV urogram is useful in showing non relationship of the right upper quadrant mass to the right kidney and no evidence of polycystic disease of the kidneys.

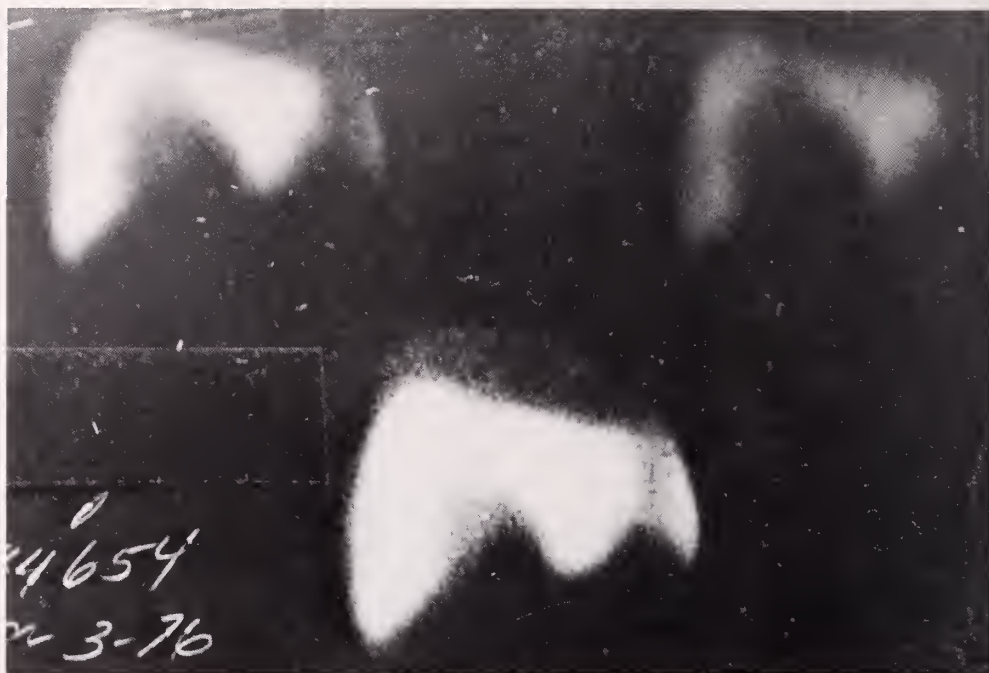
The isotope liver scan is perhaps the most useful current diagnostic imaging test in localizing the right upper quadrant mass to the liver but gives little specificity to whether this intra-hepatic mass is solid or cystic. This information can be obtained from a celiac or hepatic contrast angiography demonstrating the avascular and presumably cystic nature of the intrahepatic lesion. A two stage isotope scan with dynamic "hepatic flow study" is helpful in this respect. More recently abdominal ultrasound scanning has been found to be useful showing a typical cystic ultrasonogram pattern within or undistinguished from the liver. This non-invasive technique is rapidly performed, and the combination of isotope and ultrasound scan has been praised at a recent nuclear medicine symposium\* in a case similar to the one we are presenting here. In the near future, the CT scan will certainly add a new dimension to the diagnostic imaging technique, as has already been reported on multiple occasions.

#### CONCLUSION

A case of solitary non-parasitic cyst of the liver is reported with comments regarding the clinical and diagnostic features of this entity.

\*Nuclear Medicine Symposium, Manchester, N.H., October 1976.

Rt. Ant. Lt.



Post. Rt. Lat. Ant.

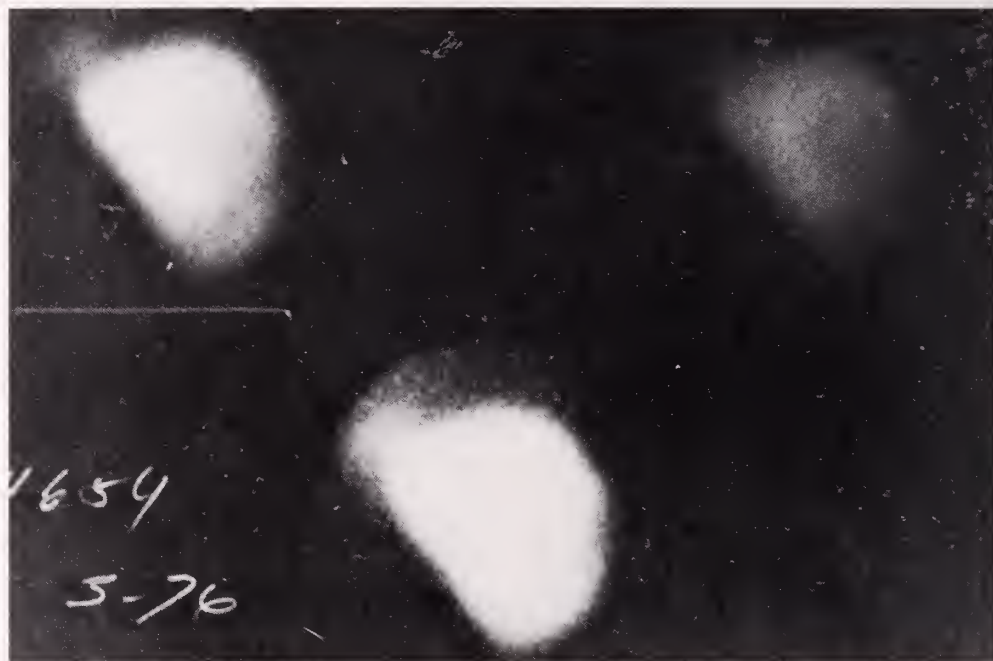


Fig. 2. Liver Scan. Large filling defect of the anterior and inferior aspect of the liver.

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LIVER-PANC. 11CM^IC



LIVER-PANC. 5\_R



Figs. 3 and 4. Transverse and longitudinal ultrasonogram of the right upper quadrant of the abdomen shows a typical cystic pattern of the mass.

## Propoxyphene: A Review

RUSSELL R. MILLER, Pharm.D., Ph.D.

Propoxyphene (PRX) is a mild analgesic that is structurally closely related to the narcotic analgesic methadone. The substance denoted by the official generic name "propoxyphene" is the alpha-dextrorotatory isomer. PRX rapidly gained wide acceptance after its introduction in 1957 and continues to be among the five most frequently prescribed drugs. This review will provide a critical analysis of information on PRX that has been published since its introduction. The objectives are to provide a comprehensive overview of the place of PRX in contemporary therapeutics and to give an analysis of its abuse, misuse, and overdosage.

### CHEMISTRY

PRX is 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionyxybutane. Its structural similarity to methadone is shown in Fig. 1.

The PRX molecule has two centers of asymmetry and exists as four stereoisomers. Of these, the alpha-dextrorotatory isomer, dextropropoxyphene, is analgesic; the alpha-levorotatory isomer, levo-propoxyphene, has antitussive activity. The beta-distereoisomers are largely inactive as therapeutic agents and cannot be readily converted into the alpha-distereoisomers. None of the isomers can be converted to methadone.

The hydrochloride salt of propoxyphene (PRX HCl) is very water soluble (> 2 gm/ml) and has a strong local anesthetic action on the tongue, as well as a very bitter taste. Propoxyphene napsylate (PRX Nap) is only slightly soluble in water (1.5 mg/ml) and has only a slightly bitter taste. The napsylate salt was introduced in 1971.

When PRX HCl and aspirin are mixed together as dry powders, free salicylic acid is produced relatively rapidly; PRX apparently catalyzes the decomposition of aspirin. In the early commercial formulations of PRX with aspirin, phenacetin, and caffeine (Darvon® Compound and Darvon® Compound-65) the PRX was placed in a coated pellet to remove it from contact with aspirin. Since these formulations provided a means for readily ob-

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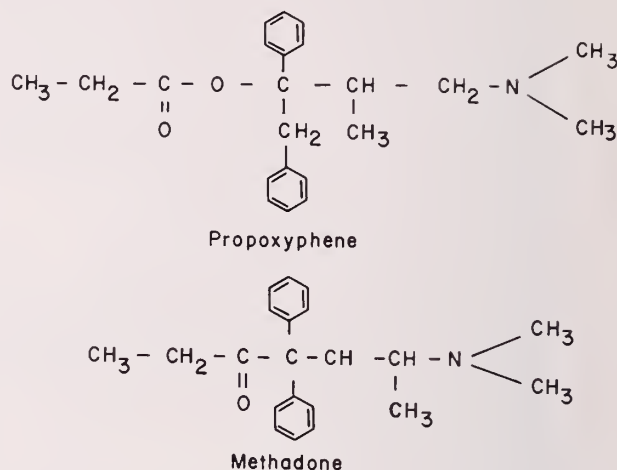


Fig. 1. Structural formulas for propoxyphene and methadone.

taining pure PRX for abuse purposes, the manufacturer, Eli Lilly & Company, reformulated Darvon mixtures so that the PRX was uniformly distributed throughout the capsule. Currently marketed Lilly mixtures have excellent stability characteristics even though the PRX is no longer physically separated from the aspirin. When the patent on PRX HCl expired in 1971, numerous other manufacturers introduced PRX products; some of the PRX-aspirin mixtures have a PRX pellet similar to that used in the original Darvon Compound formulations. In addition to this disadvantage, some of the newer product formulations may not have good aspirin stability.<sup>1</sup>

PRX Nap does not catalyze the decomposition of aspirin to any appreciable extent.<sup>2</sup> Therefore, it can be formulated with aspirin in compressed tablets.

### METABOLISM AND PHARMACOKINETICS

After oral administration PRX HCl is rapidly absorbed. Using data published in a paper by Verebely and Inturrisi,<sup>3</sup> the absorption half-life was calculated to be 31.9 minutes. Peak blood levels of PRX are attained in one to two hours.<sup>3-4</sup> The dosage form used apparently has little effect on absorption since capsules and solution of PRX HCl achieve peak plasma levels at approximately the same time.<sup>5</sup> The napsylate salt is absorbed somewhat less rapidly; peak plasma concentrations are reached in three to four hours.<sup>4</sup> PRX Nap suspension provides higher plasma concentrations at one hour after ingestion than does a tablet or a capsule.

PRX apparently has a relatively low systemic

availability after oral administration; this has been attributed primarily to metabolism on the first pass through the liver.<sup>6</sup> At the usual dose of 65 mg of the hydrochloride salt, only about 18% of the PRX reaches the systemic circulation unaltered.

The major route of biotransformation of PRX is mono-N-demethylation to norpropoxyphene, a secondary amine.<sup>7-9</sup> Seven other urinary metabolites have been identified,<sup>10</sup> but they appear to be relatively unimportant. The pharmacologic activity of norpropoxyphene is unknown as is the significance of its rather long persistence in plasma. About 7% of PRX is excreted in the intact form in 48 hours; therefore, it appears that most of the drug is eliminated as metabolites.

Plasma level studies for as long as 240 hours after single oral doses of 300 mg of PRX Nap or 195 mg of PRX HCl have shown that PRX itself has an overall mean half-life of 11.8 hours while norpropoxyphene has an apparent half-life of 36.6 hours.<sup>4</sup> These values were recently determined by means of chemical ionization mass fragmentography. Earlier studies, involving shorter observation periods and less sensitive assay methods, indicated shorter half-lives (eg 3.0 hours<sup>3</sup> and 6.6 hours<sup>11</sup> for PRX and 16.8 hours for norpropoxyphene.<sup>3</sup>)

In all of the plasma level studies substantial inter-subject differences in the levels of PRX and norpropoxyphene were observed. Thus, some patients that receive a usual dose of PRX (eg, 65 mg of the hydrochloride) may achieve effective drug concentrations in the central nervous system while others may not.<sup>3</sup> This may account for some of the difficulties in measuring the analgesic efficacy of PRX.

Equimolar doses of PRX as the hydrochloride and as the napsylate provide similar plasma concentrations. The differences between salts are very small in comparison with those among subjects and among doses.<sup>12</sup>

Repeated doses of PRX HCl and napsylate at six-hour intervals lead to increasing plasma concentrations with a plateau after the ninth dose at 48 hours.<sup>12</sup> The plateau is reached at about the same time regardless of the doses given, but the plateau plasma concentration is higher when larger doses of either PRX HCl or PRX Nap are given.<sup>12</sup>

In a controlled clinical trial analgesia scores and plasma concentrations of PRX were not significantly correlated when all of the pairs of individual observations were included in the computation.<sup>13</sup> However, the scores and plasma concentrations were related to the amount of drug given, and on this basis the means of the analgesia scores and plasma concentrations were significantly correlated. Additional studies are needed to determine if measurement of plasma PRX concentrations is clinically useful.

The metabolism of PRX may be accelerated by substances in cigarette smoke, since a decreased efficacy of PRX has been noted when cigarette smokers were compared to nonsmokers.<sup>14</sup> A linear

increase in the proportion of ineffective ratings of about 5% for each pack of 20 cigarettes smoked per day was observed.

Three cases of a possible interaction between Distalgesic, a combination of PRX HCl and acetaminophen, and warfarin have been reported.<sup>15,16</sup> Hematuria was observed in all cases. Inhibition of the metabolism of warfarin by PRX was postulated to be the cause of the bleeding.

An interaction between PRX and orphenadrine, consisting of confusion, anxiety and tremors, has been reported in a few patients,<sup>17</sup> but it has not been clearly established.<sup>18,19</sup>

The bioavailability of ten commercial products of PRX HCl capsules has been studied and no significant differences were noted in plasma levels at 1, 2, 3, 4, 6, 8, and 12 hours, peak plasma levels, time to achieve peak plasma level, and area under the plasma level-time curve.<sup>20</sup>

#### ANALGESIC EFFICACY OF PRX HCL AND PRX NAP

Twenty published double-blind studies of the analgesic efficacy of PRX HCl were evaluated by Miller, Feingold, and Paxinos<sup>21</sup> in a review published in 1970. Since further comment on these earlier studies is unnecessary, the following discussion is primarily concerned with English-language studies published after the period covered by the above cited review.

Thirteen additional double-blind studies have been published; they are described in Table 1.<sup>22-34</sup> In four of these studies PRX HCl and PRX Nap were the only drugs evaluated; other analgesics were not included.<sup>22,24,27,32</sup> Three of these studies showed no significant difference between equimolar doses of the two propoxyphene salts in most measures of efficacy; in one study PRX Nap appeared to be 1.25 to 1.49 times more effective than PRX HCl. In the three studies where a placebo control was used, PRX was significantly superior to the placebo.

Another study of PRX Nap and HCl included enteric-coated aspirin.<sup>23</sup> In this study the investigators either did not make a statistical comparison of the efficacy of aspirin and the PRX salts or made the comparison and chose not to present it in their paper. Such a comparison undoubtedly would have found that the total analgesic scores for enteric-coated aspirin 650 mg were significantly superior to the scores for PRX HCl 65 mg and PRX Nap 100 mg. Such a difference can be statistically demonstrated using data provided in the paper, but this is not an appropriate procedure since any statistician who had seen the published article would be biased.

In the eight remaining studies,<sup>25,26,28,29,30,31,33,34</sup> PRX was not shown to be superior to other analgesics, and in three of the studies PRX appeared to be no better than placebo.<sup>25,26,30</sup> One of the studies showing no analgesic effect of PRX<sup>30</sup> received considerable publicity and led to two "Dear Doctor" letters from the manufacturer of Darvon (PRX HCl, Eli Lilly and Company) and letters to the editor.<sup>35</sup>

TABLE 1

DOUBLE-BLIND CLINICAL STUDIES OF PROPOXYPHENE								
Reference		Drug <sup>a</sup> and Strength (mg)	Placebo Control ? (or trials)	No. of Patients	Type of Pain	Frequency of Administration	Frequency of Efficacy Measurements	Conclusions on Efficacy
1	22	PRX HCl (50,100,200) PRX Nap (75,150,300)	Yes	532	Postpartum	Single dose	1,2,3,4,6,8 hrs (by observer)	No difference between equivalent doses of PRX HCl and PRX Nap at 1,2,3 and 4 hrs; both drugs superior to placebo.
2	23	PRX HCl (65,130) PRX Nap (100,200) EC ASP (325,650)	Yes	300	Postpartum	Single dose	1,2,3,4,6,8 hrs (by observer)	No difference between equivalent doses of PRX HCl and PRX Nap. PRX Nap greater at 6 and 8 hrs. All drugs superior to placebo.
3	24	PRX HCl (32,65,130) PRX Nap (50,100,200)	Yes	336	Postpartum	Single dose	1,2,3,4,6,8 hrs (by observer)	No difference between equivalent doses of PRX HCl and PRX Nap. Both drugs superior to placebo.
4	25	COD (32) COD (32) + APC MEP (32) MEP (32) + APC PRX HCl (32) PRX HCl (32) + APC APC	Yes	928	Postpartum	4 times a day	24 hours (by observer)	No difference between drugs and placebo.
5	26	ACET (650) PRX HCl (65) ACET (650) + PRX HCl (65)	Yes	200	Postpartum	Single dose	½,1,2,3,4 hrs (by observer)	ACET and combination of ACET and PRX HCl superior to PRX HCl and placebo. No difference between PRX HCl and placebo in two of three evaluations. No difference between ACET and combination.
6	27	PRX HCl (65) PRX Nap (100)	No	160	Mixed chronic	Variable	1 measurement at time drug discontinued (by observer)	No difference between PRX HCl and PRX Nap.
7	28	PRX HCl (65) ASP (650) PTZ (50)	No	225	Postpartum	Single dose	½,1,2,3,4 hrs	ASP and PTZ superior to PRX.
8	29	CPH (800) PRX HCl (65) ASP (650)	No	92	Musculo-skeletal	3 or 4 times a day	24,72 hours (by observer)	No difference between drugs.
9	30	MEF (250) PTZ (50) ACET (650) PHEN (650) COD (65) PRX HCl (65) ETHO (75) PROM (25)	Yes	57	Cancer	Variable	Variable (by patient)	ASP superior to all agents. MEF, PTZ, ACET, PHEN and COD superior to placebo. No difference between PRX, ETHO, PROM, and placebo.
10	31	MEF (250) PRX HCl (60) MEF (250) + PRX HCl (40)	Yes	16	Osteo-articular	3 times a day for 2 days	Unspecified time "after treatment" (by observer)	No difference between MEF, PRX, and combination. All drugs superior to placebo.
11	32	PRX HCl (32,65,130) PRX Nap (50,100,200)	Yes	342	Mixed	Single dose	½,1,2,3,4,5,6 hrs (by observer)	PRX HCl (65,130) and PRX Nap (50,100,200) superior to placebo. No difference between equivalent doses of PRX HCl and PRX Nap in most measures.
12	33	PRX HCl (65) IBP (400)	No	70	Postpartum	Single dose	½,1,1½,2,3,4,5,6,7,8,9,10,11,12 hrs	IBP superior to PRX.
13	34	PRX Nap (100) PRX Nap (200) ASP (325) ASP (650) PRX Nap (100) + ASP (325) PRX Nap (200) + ASP (650)	Yes	57	?	Single dose	1,2,3,4,5,6 hrs (by observer)	PRX Nap (200) + ASP (650), ASP (650), and PRX Nap (200) superior to placebo. No difference between other drug and placebo.

<sup>a</sup>Abbreviations for drugs: PRX HCl — propoxyphene hydrochloride, PRX Nap — propoxyphene napsylate, EC ASP — enteric-coated aspirin, ACET — acetaminophen, MEF — mefenamic acid, PTZ — pentazocine, COD — codeine, PHEN — phenacetin, ETHO — ethoheptazine, PROM — promazine, CPH — chlorphenesin, MEP — meperidine, APC — aspirin, phenacetin, and caffeine, IBP — ibuprofen.

TABLE 2

COMBINATION PRODUCTS CONTAINING PROPOXYPHENE HYDROCHLORIDE OR PROPOXYPHENE NAPSYLATE	
Trademark Names	Ingredients
1. Darvon® Compound	Propoxyphene Hydrochloride 32 mg Aspirin 227 mg Phenacetin 162 mg Caffeine 32.4 mg
2. Darvon® Compound-65 Dolene Compound-65 SK-65® and others	Propoxyphene Hydrochloride 65 mg Aspirin 227 mg Phenacetin 162 mg Caffeine 32.4 mg
3. Darvon® with A.S.A.®	Propoxyphene Hydrochloride 65 mg Aspirin 325 mg
4. Darvon-N® with A.S.A.®	Propoxyphene Napsylate 100 mg Aspirin 325 mg
5. Darvocet-N®	Propoxyphene Napsylate 50 mg Acetaminophen 325 mg
6. Darvocet-N® 100	Propoxyphene Napsylate 100 mg Acetaminophen 650 mg

Some of the above studies have design deficiencies; they include: (1) absence of placebo control, (2) inclusion of patients without demonstrated pain, (3) variable frequency of drug administration, (4) variable or infrequent efficacy measurements, and (5) possible concomitant administration of other drugs affecting the central nervous system. However, most of the studies do not have serious defects and, in general, they appear to have been better designed than those studies covered by the previous review of Miller, Feingold, and Paxinos.<sup>21</sup>

#### ANALGESIC EFFICACY OF COMBINATIONS OF PRX WITH OTHER ANALGESICS

Six combination products containing PRX HCl or PRX Nap are currently being marketed in the United States; they are described in Table 2.

*PRX with Aspirin, Phenacetin, and Caffeine.* Darvon Compound-65 and similar trademarked products are prescribed more frequently than all other PRX products, including the single-entity preparations. In view of this popularity, it is remarkable that only five known double-blind studies of PRX with aspirin, phenacetin, and caffeine (APC) have been published;<sup>25,36-39</sup> these studies are described in Table 3 (numbers 1-5). The combination of PRX with APC was not compared with PRX 65 mg alone in any of these studies. The combination was compared with APC alone in two studies,<sup>25,37</sup> and in one of these,<sup>37</sup> PRX Nap plus APC appeared to be superior to APC alone. The remaining three studies<sup>36,38,39</sup> are of little value because they compared the combination of PRX and APC with other combinations, rather than single-entity drugs; no significant difference between combinations was reported in any of these studies.

*PRX with Acetaminophen.* The efficacy of PRX with acetaminophen has been investigated in three double-blind studies;<sup>26,40,41</sup> they are described in Table 3 (numbers 6-8). Two of these studies<sup>40,41</sup> are of little value since they did not compare the PRX-acetaminophen mixture with either PRX or acetaminophen alone. The remaining investigation<sup>26</sup>

showed no difference between the combination of PRX and acetaminophen and acetaminophen (650 mg) alone.

*PRX with Aspirin.* The efficacy of PRX with aspirin has been examined in four double-blind studies;<sup>34,36,42,43</sup> they are described in Table 3 (numbers 1,9-11). Study number 1<sup>36</sup> compared PRX plus aspirin with another combination; thus, it is of little value. In studies 9 and 11 combinations of PRX and aspirin with quantities of drugs that are different from those marketed in the United States were compared to single-entity drugs. In addition to this drawback, both of these studies have serious design deficiencies which preclude drawing any useful conclusions from them. In study 10 PRX Nap 100 mg plus aspirin 650 mg was compared to other combinations and aspirin 650 mg alone. This well-designed study showed no difference between plain aspirin and PRX Nap with aspirin.

In summary, there is little evidence that combinations of PRX with other analgesics are superior to one analgesic alone. Aspirin or acetaminophen appear to be just as effective when given alone as when given with PRX.

#### NON-ANALGESIC USES OF PRX

PRX Nap has been used in acute detoxification and maintenance treatment of heroin addicts.<sup>44-46</sup> In inpatient and outpatient detoxification programs, divided daily doses of 600 to 1400 mg of PRX Nap have been used. When used to maintain former heroin addicts, single daily doses of 400 to 1500 mg have been used; the initial dose is 200 to 400 mg/day.

PRX Nap has also been used as a supplemental agent in methadone detoxification programs.<sup>46</sup> In using methadone for heroin detoxification in recommended decremental dosage, severe opioid-like withdrawal symptoms are sometimes observed. By giving PRX Nap during methadone withdrawal, these symptoms are avoided; PRX Nap can then be withdrawn with few physical complaints.

PRX Nap appears to have some advantages over methadone in the treatment of narcotic addicts. Side effects of PRX are minimal in the usually employed doses; the lessened libido and male impotence observed with methadone is not a significant problem with PRX Nap. Methadone is a physically-addicting drug and withdrawal phenomena are common; withdrawal problems are rare with PRX Nap. In view of these and other possible advantages, PRX Nap should be further evaluated for its effectiveness and safety in the treatment of narcotic addicts. The relative efficacy of PRX Nap compared to methadone is presently unknown.

#### ADVERSE EFFECTS

The adverse effects of PRX in hospitalized medical patients are few and minor.<sup>21,27,47</sup> They include minor gastrointestinal complaints (nausea, vomiting, etc.), central nervous system symptoms (ver-

*Continued on Page 103*

# Every Man's Guide to the Treatment of Diabetic Retinopathy

KENNETH P. WOLF, M.D.

In the not too distant past, the above title would have omitted the use of the word "treatment" because there simply was none! Exhorting patients to carefully manage their diabetes and thereby hoping to reduce the incidence of diabetic retinopathy was the approach of the day. No studies, however, showed a statistically significant difference between well regulated and poorly regulated diabetics in regard to their visual prognosis. Meanwhile, the number of diabetics and consequent retinopathy and blindness increased at a rapid rate with the incidence of diabetes mellitus doubling every fifteen years.<sup>1</sup> From 1965 to 1973, there was an increase of 50% in the total number of diabetics in this country and in 1974 alone there were 600,000 new cases of diabetes diagnosed.<sup>2</sup> Improved medical care had kept the diabetic alive and reproduction had spread the gene in an even widening circle such that at the present time each American has one chance in five of developing diabetes during his lifetime.<sup>3</sup> The 200,000 visually and thereby economically handicapped diabetics will grow to more than 500,000 over the next ten years.<sup>4</sup>

Diabetes has become a major cause of visual impairment and threatens to become, or perhaps already has become, the number one cause of visual impairment in the United States today. The advent of laser therapy, however, offers a new modality for therapy of diabetic retinopathy and the recently released results of the Diabetic Retinopathy Study, under the sponsorship of the National Eye Institute, offers very convincing evidence that such treatment is effective in certain types of diabetic retinopathy. A reported 61% reduction of severe visual loss over a two-year followup, in the treated eye compared to its fellow controlled eye in the randomized controlled clinical trial involving over 1700 patients, strongly suggests the efficacy of this treatment modality.<sup>5</sup> It appears that laser therapy and other forms of photocoagulation techniques are evolving as the mainstay of effective diabetic retinopathy therapy and will be with us for some years to come.

The purpose of this paper is to give an over-view of diabetic retinopathy for the non-ophthalmologist with the hope that a further awareness of the problem and its treatment will result in more patients receiving earlier and consequently more effective care.

Of the estimated five to ten million diabetics in this country, approximately one-half will develop diabetic retinopathy. The longer a diabetic lives with his condition the greater the chance of his developing retinopathy. Approximately 3 out of 4

diabetics who live with the disease for 15 years will show evidence of diabetic retinopathy.<sup>6</sup>

Diabetic retinopathy is classified into two major categories. The first of these is non-proliferative or background retinopathy and this accounts for approximately 60% of all diabetic retinopathy. It is characterized by the presence of microaneurysms, hemorrhages, hard exudates, and retinal edema. Specifically, however, there is no evidence of new vessel proliferation either on or in front of the retinal surface. Leakage at the capillary level, either from the microaneurysms themselves or from other areas of incompetent microvasculature, results in the classic blot and dot hemorrhages of diabetic retinopathy. Retinal edema, again a reflection of vascular incompetence, is characterized by a milky whitish discoloration of the retina. A subsequent loss of transparency of the retina results in blockage of the normally seen underlying choroidal vascular pattern. In addition, leakage of lipid rich material results in collection of the classic hard yellow exudates seen in diabetic retinopathy. These exudates have been shown to be destructive to retinal architecture and deposits of such hard exudates in and around the macula usually results in permanent decrease in acuity even if they later resorb following therapy. The larger (approximately  $\frac{1}{3}$  disc diameter) soft, cotton-wool exudates with indistinct borders, seen occasionally with diabetes, represent localized areas of retinal ischemia. These cotton-wool spots are seen more frequently with hypertensive retinopathy, but localized areas of capillary destruction and shutdown seen with diabetic retinopathy result in these areas of ischemic cotton-wool spots making their appearance in this disease also. The diabetic with mild background retinopathy presenting with a few microaneurysms and occasional hemorrhages or exudates removed from the macular region, is usually visually unimpaired. Once, however, incompetent microvascular circulation results in edema in the macular region, or exudates deposit themselves in the macular region, then the vision slowly starts to fall. Unilateral onset of decreased acuity may not be noted by the patient and unless the examining physician routinely checks the patient's vision, then the disease process may not be recognized in its early most treatable phase. Further progression and development of the disease process in the second eye then brings the patient directly to the ophthalmologist. Providing that no irreversible retinal cystic changes secondary to edema have occurred, and further that there is no significant deposit of exudative material in the

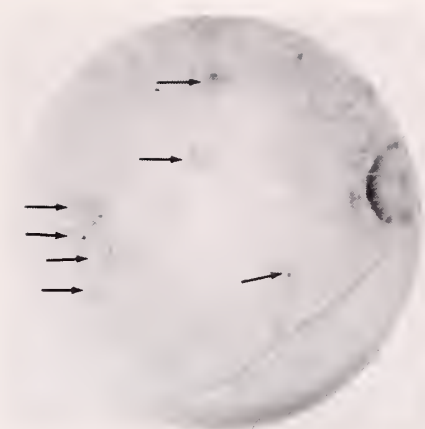
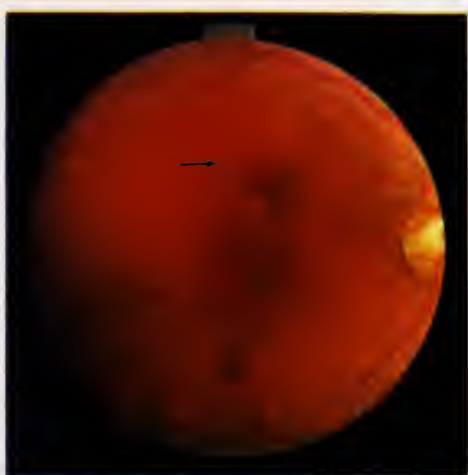


Fig. 1. BACKGROUND RETINOPATHY — On the left is the fundus of a 30-year-old girl showing one small hemorrhage above the macula (see arrow) secondary to diabetic retinopathy. On the right is the angiogram of the same patient showing scattered collections of dye material appearing around the macular region, which are not visualized on fundus examination with the ophthalmoscope. As this fluid continues to collect, the macula may well become edematous with subsequent decrease in visual acuity. Note the discrepancy between the very benign appearing fundus picture on ophthalmoscopy and the angiographic evidence of a more advanced process actually occurring in this patient. (Photos and angiogram courtesy of Mr. Philip K. Chin)

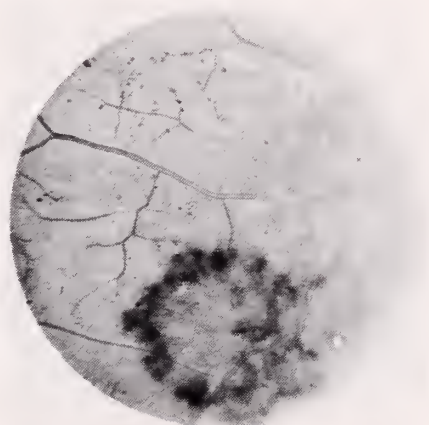


Fig. 2. PROLIFERATIVE RETINOPATHY — On the left is the fundus of a diabetic of nine years' duration showing one discreet area of flat neovascularization radiating out in all directions from a central feeding vessel (located within the encircled area). Note that this lesion could be easily missed without a thorough study of the fundus on dilated ophthalmoscopy. On the right is a fluorescein angiogram (not from the same patient) showing massive leakage of dye from a similar lesion.

Fig. 3. PROLIFERATIVE RETINOPATHY, POST-TREATMENT — At right one sees pigmented scars post-treatment with the laser which has destroyed an area of neovascularization similar to that shown on Figure 2 above. As is usually the case, the patient is unaware of any abnormality in the visual field secondary to the treatment. (Slide courtesy of J.S. Tchao, M.D.)



macular region, then one can consider the use of laser to "spot weld" the leakage sites. Non-proliferative retinopathy is most treatable in its earliest stages when vision has not precipitously decreased and not when there is massive exudate, hemorrhage, and edema present. Fixing the leaky basement plumbing six months later, so-to-speak, will do nothing to restore the water-logged playroom furniture. Early treatment is imperative to prevent irreversible damage.

The second form of diabetic retinopathy is proliferative retinopathy which accounts for about 40% of all diabetic retinopathy. Simply stated, if a patient has new vessels growing either on the surface of the retina or out into the vitreous overlying the retina, then he is classified as having proliferative retinopathy. He may or may not also have accompanying background or non-proliferative retinopathy as well. In many cases, the patient starts with non-proliferative retinopathy and then as proliferative retinopathy appears at a later stage, the non-proliferative component may subside. The visual loss in non-proliferative retinopathy comes from impaired retinal function due to the presence of edema and exudates and hemorrhages with a consequent drop in acuity, such that many of the everyday tasks such as reading or driving a car become impossible. The patient with proliferative retinopathy, however, is faced with possible total blindness from massive hemorrhaging occurring from these areas of incompetent new vessels. This hemorrhagic event can fill the vitreous with blood precluding either the patient seeing the world around him or the examiner seeing into the patient's eye. Secondary vitreous scarring and contracture due to the presence of such blood then causes traction on the adherent retina and detaches it without significant hope of effective surgical repair. The presence of new vessels randomly growing across the retinal surface should alert the practitioner to the impending potential disaster because the prognosis, both for vision and for life itself, is not good when the patient presents with proliferative retinopathy. Fifty percent of these patients will be dead within five years and of those still alive half will be blind if they have not been treated by photocoagulation.<sup>7</sup> They will live on the average of six to seven years before probably succumbing to other complications of their generalized disease. The therapeutic approach in proliferative retinopathy therefore, is to attempt to keep these people seeing for the remainder of their days by eradicating these areas of neovascularization through the use of laser, sealing off these new vessels before they rupture and cause a vitreous hemorrhage and subsequent blindness. In some cases, especially when the neovascularization lies on or in front of the optic nerve head, one does not directly attack the areas of neovascularization for fear of rupturing these vessels at the time of treatment as well as for fear of damaging the underlying optic nerve. The therapeutic approach in these

cases, known as panphotocoagulation, involves indirectly treating these vessels by randomly placing 1500 to 3000 laser burns in the retinal structure in a scatter fashion, destroying up to 30% of the retinal architecture. The consequent decrease in oxygen demand results in regression of the neovascularization in a significant number of cases. Surprisingly, the subjective response on the part of the patient is such that he is not usually aware of these microscopic (100 micron to 1000 micron) retinal burns. Essentially normal visual fields after therapy confirm the surprisingly benign nature of this ablation technique of laser therapy. With proliferative retinopathy, the approach is to treat and cause regression of the areas of neovascularization before they hemorrhage impairing the patient's vision and precluding, in many cases, any attempts at subsequent therapy.

The two technical advances which now allow for treatment of diabetic retinopathy are fluorescein angiography and laser photocoagulation systems. The fluorescein angiography involves intravenous infusion of fluorescein dye with subsequent rapid sequence retinal photography to demonstrate the areas from which the dye is leaking. This diagnostic tool is imperative in as much as it accurately locates the multiple leaking sites in the retina which can then be coagulated with minute laser burns. The Argon laser itself (which first commercially became available in 1971) offers distinct advantages over previous light coagulating systems. First, spot sizes are as small as 50 microns (approximately 1/500 inch). Thus, during treatment only areas of involvement are coagulated and no normal tissue need be needlessly sacrificed. This becomes important when one is applying several hundred burns in as much as significant areas of normal tissue would otherwise be destroyed. Also the power levels generated are far greater than previously possible, thereby allowing one to treat with some degree of effectiveness even through optical opacities such as mild cataracts or mild vitreous hemorrhage. Previous white light systems containing all wave lengths of light have the potential for coagulating other structures within the eye not meant for therapy as opposed to the monochromatic laser which allows more selective therapy. Armed, therefore, with fluorescein angiography for diagnostic maneuvers and laser photocoagulators for therapy, the ophthalmologist is now capable of locating and treating even the most minute leaks as well as coagulating large areas of neovascularization in an attempt to preclude visual loss.

What then are the conclusions to be drawn from this by the primary care practitioner and others who deal with diabetics? First, diabetic retinopathy is treatable. The greatest chance of success comes with the patient being treated before irreversible retinal changes from long-standing edema, exudate formation, vitreous hemorrhage, and retinal de-

*Continued on Page 102*



# Maine Blue Cross and Blue Shield News

## I.D. CARDS CHANGED

You will begin to see a change in subscriber identification cards as new cards are issued to existing subscribers who change their coverage or as new subscribers join.

We are cooperating in an effort to standardize the card throughout the country, but we have employed the "phased in" approach to avoid incurring excessive start-up costs for the new card. In other words, for a year, or even more, you will be seeing both the old-style card, which spells out the Blue Shield coverage the subscriber holds, and the new card, which shows the Blue Shield coverage in code.

The key to the Blue Shield coverage code is on the back of every new card, and reads as follows:

### B.S. (Blue Shield)

C — \$350 Schedule

D — \$450 Schedule

E — \$1850 Schedule

G — 80% UCR

R — 100% UCR



N — National Account

The code will be computer typed under "BS Level" on the front of new cards. With the space limitations imposed by the national I.D. standards, we did not have room to indicate the level of Blue Cross coverage on the card, but it is printed on the stub of the I.D. card mailer for the subscriber. This information is available from us to providers who need the Blue Cross level to initiate a claim.

The basic reason for the change to a national standardized I.D. card is to facilitate out-of-state recognition of the card. Also, the Blue Cross and Blue Shield of Maine code number on the face of the card will help the out-of-state Blue Cross or Blue Shield Plan recognize the "home" Plan.

The new card is also smaller, so that it will fit into a wallet easier and not become as "dog-eared" as some of the older cards have.

We hope the transition to our new card format will be easy for you, and a reproduction of the card face is shown here so that you will recognize the new card as it begins to appear.

			
SUBSCRIBER NAME			
CERTIFICATE NUMBER			
GROUP NUMBER	BS PLAN CODE	BC PLAN CODE	
BS LEVEL	BENEFIT RIDERS	BAMICO	

# Pseudo Double Pylorus

GEORGE E. DAVIS, M.D.,\* JOHN W. CARRIER, M.D.\*\*  
and OSCAR O. CABATINGAN, M.D.†

Engle described "A recognizable roentgen pattern" for the double pyloric canal seen rarely in pyloroduodenal ulcer disease.<sup>1</sup> In the same issue of *Radiology*, Bender and Soffa added another case (bringing the total described to nine) and stated that the "radiographs are characteristic, but may be difficult to interpret if one is not familiar with the entity."<sup>2</sup> They also cautiously added that mucosal

folds, polyps, or other tumors could mimic this entity.

The purpose of this paper is to underscore the need for gastroscopy to clinch or refute the double pylorus pattern. The following photographs show yet another patient (Y.A. referred by the third author) which seems to clearly duplicate similar UGI films in Engle's paper. Upon investigation with the Olympus GIF however, one can see that as the instrument tip advances, the apparent double channel disappears revealing a single pylorus divided by an edematous fold probably containing scar tissue.

## REFERENCES

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Fig. 1. Overhead view of the apparent double pylorus.

Fig. 2. Close-up view of apparent double pylorus.

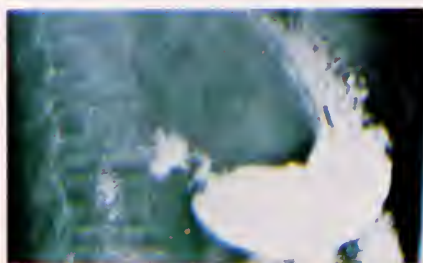


Fig. 1



Fig. 2

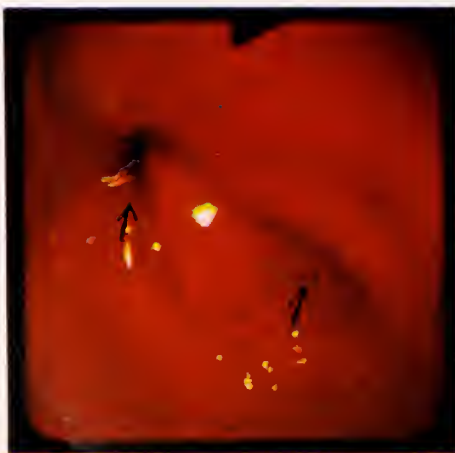


Fig. 3

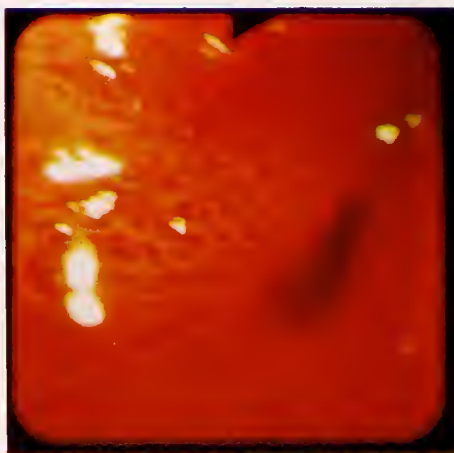


Fig. 4

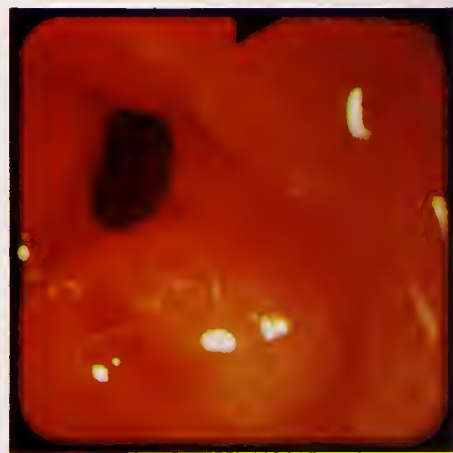


Fig. 5

Fig. 3. Apparent double pylorus as seen endoscopically from antrum. Arrows show potential channels.

Fig. 4. Edematous mass of antral mucosa seen while approaching the true pylorus.

Fig. 5. True singular pylorus seen after retracting scarred edematous antral mucosa.

When Big Ben looks "a little off"...

# Antivert<sup>®</sup>/25 (meclizine HCl) 25 mg. Tablets for vertigo\*

■ **Most Widely Prescribed**—Antivert is the most widely prescribed agent for the management of vertigo\* associated with diseases affecting the vestibular system such as Menière's disease, labyrinthitis, and vestibular neuronitis.

■ **Relief of Nausea and Vomiting**—Antivert/25 can relieve the nausea and vomiting often associated with vertigo.\*

■ **Dosage for Vertigo\***—The usual adult dosage for Antivert/25 is one tablet t.i.d.

#### BRIEF SUMMARY OF PRESCRIBING INFORMATION

**\*INDICATIONS.** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

**Effective:** Management of nausea and vomiting and dizziness associated with motion sickness.

**Possibly Effective:** Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

**CONTRAINDICATIONS.** Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

**WARNINGS.** Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

**Usage in Children:** Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

**Usage in Pregnancy:** See "Contraindications."

**ADVERSE REACTIONS.** Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

More detailed professional information available on request.

**ROERIG**   
A division of Pfizer Pharmaceuticals  
New York New York 10017



DAVID E. SMITH  
COMMISSIONER

## Maine Department of Human Services

# Disease Reporting in Maine: Method and Purpose

WILLIAM NERSESIAN, M.D.\*

On the fourth of July weekend, 1976, a large resort inn in southern Maine experienced an outbreak of Salmonellosis involving eighty people. All patients were ill within a 24-hour period and many required hospitalization. Local physicians and State health officials had no problem identifying this as an epidemic; the entire matter was obvious to all present. Unfortunately, this is not always the case.

A small private school also experienced a Salmonella outbreak in October 1976, involving at least ten people over several weeks. Only two students were hospitalized, each at a different medical center. Several of the cases were relatively mild and some were told at a local emergency room that they had a case of "flu." A few patients never saw a physician. Only after one of the hospitalized cases was reported to the State Bureau of Health was an investigation begun which uncovered the other cases. The school kitchen was statistically implicated as the source of infection.

The chief benefit of the epidemiology done in both of these cases was the prevention of further cases. In addition, patient education was done to prevent secondary cases. If the initial single case had not been reported in the school Salmonella outbreak, perhaps many additional persons may have become ill.

Disease reporting is a necessary component of any Public Health system. The rationale for the accumulation of data and the ensuing epidemiological investigation are:

1. *Disease Prevention Has an Important Place in Modern Medicine.* In the long run, it is more beneficial to people and less costly to society if disease can be prevented before it occurs. By seeking the source of infectious disease, the epidemiological process attempts to accomplish this.

2. *Very Few Physicians Have the Time to Spare for Complete Epidemiological Investigation.* As an example, when we are notified of a case of hepatitis, we interview the patient when possible, and ask regarding recent exposures to tattooing,

acupuncture, transfusions of blood products, surgery, oral surgery or dental work, raw clams or oysters, or other patients with hepatitis. If gamma globulin would be helpful to the patient's immediate family or close contacts, we suggest this and even donate the globulin to indigent patients. We educate the patient regarding his condition and the potential dangers he poses to others if his habits are careless. Food handlers or child care workers are prohibited from work until they have recuperated. All hepatitis cases are plotted on a map of Maine to detect trends or possible epidemics. Finally, a copy of our interview is forwarded to the local health officer and another copy to the National Center for Disease Control so that more can be learned about the transmission of this disease. While there is no question that the average Maine physician is quite capable of caring for and educating his patients, he very seldom has the time for *everything that could be done* to prevent further cases.

3. *It is Often Very Difficult to Detect an Epidemic at the Ground Level.* As in the example of Salmonella at a private school, many patients with mild symptoms may not see a physician at all. Some will see a public health nurse, an industrial nurse or school nurse. Some may visit an emergency room. Finally, if there are several physicians in town, each may only see one or two patients with the disease and not suspect an epidemic. However, when these patients are reported to the Bureau of Health, a clustering of cases in a given area will reveal the epidemic.

4. *Disease Reporting Allows Feedback to Physicians and is a Part of Continuing Education.* The Bureau of Health mails out a monthly newsletter (the "Epi-gram") to all Physicians, school and public health nurses and local health officers in the State. The Epi-gram summarizes all infections reported to the State and seeks to keep practitioners appraised as to changes in the incidence of these diseases. Although all major epidemics are presented, the names of towns and institutions are omitted (where necessary) to preserve confidentiality. A monthly feature article in the Epi-gram

\*State Epidemiologist, Bureau of Health, Maine Department of Human Services.

*Continued on Page 98*

# From the Secretary's Notebook

## Summary of 1976 Fall Meeting of the M.M.A. House of Delegates

December 12, 1976 at Waterville, Maine

The Fall Meeting of the M.M.A. House of Delegates was held at the Mid-Maine Medical Center in Waterville on Sunday, December 12, 1976, with an attendance of 45 delegates and alternates, and nine guests. Richard C. Leck, M.D., President of the M.M.A. called the meeting to order and George W. Bostwick, M.D., Speaker of the House, presided.

### 1. Committee Reports:

a) *Liaison with the Maine Bar Association* — Dr. John Woodcock, Chairman, reported that his Committee has been studying the question of setting up Statewide malpractice screening panels. Copy of a subcommittee report (12/1/76) in this regard was given to each delegate. Dr. Emerson Drake of Portland told the delegates of the experience in Cumberland County with their screening panel. Dr. Woodcock said that the Committee plans to give a presentation to physicians and lawyers in 3 areas of the State, and asked for an endorsement of continuing this idea of Statewide screening panels, and this was *approved*.

b) *Continuing Education* — Dr. Chamberlin presented a report of the Committee on Continuing Medical Education. It requests each delegate and alternate to make a special point to discuss what the role of the M.M.A. should be in CME with his respective county, hospital and staff membership and to report the results and/or findings in writing to the Chairman of the CME Committee (H. J. Wheelwright, M.D.) at P.O. Box 250, Brunswick 04011, *no later than 15 March 1977*. It is hoped that a definite plan will be ready for presentation to the House of Delegates in April, and for vote in June.

c) *Legislation* — Brinton T. Darlington, M.D., Chairman, spoke on topics expected in the upcoming legislature — medical malpractice insurance, certificate of need, administration of medications, etc. Dr. Darlington urged cooperation from the county societies in developing a "key man" legislative program. A letter will be going out soon to all county societies in this regard.

d) *Ad Hoc Committee on Fees* — A written report by Charles H. Lightbody, M.D. was given to each delegate. Mr. Thomas Cathcart of Maine BCBS was present to speak regarding recommendations proposed for changes in the BS programs. Nine recommendations for consideration, which have been approved by the M.M.A.'s Committee on Health Care Financing, were discussed in detail by Mr. Cathcart, and a list of these given to each delegate.

2. **Report of AMA Clinical Convention** — Dr. Brinton T. Darlington, Alternate Delegate, reported on last week's meeting in Philadelphia. Highlights of the convention will appear in the December 13th issue of *American Medical News*. Dr. Darlington expressed the opinion that anyone not belonging to the AMA is taking a "free ride" on what organized medicine is doing for all physicians.

3. **Diagnosis of Death** — Dr. Henry Ryan, Chief Medical Examiner for the State of Maine, presented each delegate with a six-page report on the "Certificate of Death," covering such areas as Obligation, Time Limits, Legal Responsibility, Institutionalized Patients, Probable Cause, Medical Examiner Cases, Current Problem, Ethics of House Call at Time of Death, Current Criticism, Pronouncement of Death, Examination of the Body and Timely Certification. The report included seven *recommendations* to the M.M.A. and it is hoped this will be taken back to the county societies and a resolution brought in to the House of Delegates next April. A copy of the material is available on request to the M.M.A. office.

4. **Medical Malpractice Study Commission** — Dr. Francis I. Kittredge, our representative on the Commission, reported on current activities. Public hearings were held in November, and a third redrafting of the Commission's work is being done.

### 5. Resolutions:

a) A resolution on the President of the M.M.A. remaining on the Executive Committee for an additional period was *referred* to the April meeting of the House of Delegates.

b) The following resolution, presented by Dr. Donald J. McCrann, Jr. of Portland, was *approved*:

WHEREAS: It is necessary to make long-range plans for improving the perinatal facilities in the State of Maine, and

WHEREAS: The current statistics are suspect at best, and

WHEREAS: There are pediatricians and obstetricians interested in gathering accurate data on infant deaths, neonatal deaths, stillbirths, and maternal high risk pregnancies, morbidity and mortality; and formulating long-range recommendations based on this data,

THEREFORE BE IT RESOLVED: The MMA endorse the concept of planning based on adequate and accurate data. The MMA sponsors and fully supports the collection and analysis of data by the Special Committee on Maternal and Child Welfare or its designate, with the full understanding that no MMA funds will be spent on this project.

6. Other —

a) Dr. Francis I. Kittredge reported that in 1975, he and other Bangor physicians bought a CAT scanner, after meeting with B agencies and the State Comprehensive Health Association. Agreeing that they had a right to purchase this equipment, a fee of \$250 per scan was accepted as reasonable by third parties. After paying this for one year, the Department of Human Services has decided that they will now reimburse at the rate of \$50 per scan. The

Bangor group is going for a declaratory judgement and permanent injunction against the Department of Human Services and is asking the M.M.A. to join them in the suit. Dr. Kittredge reported that he spoke with the Executive Committee earlier today, and they will be discussing the M.M.A.'s involvement.

b) Dr. Thomas Shields asked if there was any action in regard to the M.M.A. office moving its headquarters, and Dr. Leck reported none at this point.

7. **Spring Meeting of the House of Delegates** — Sunday, March 27, 1977 in Bangor at 2:00 P.M.

8. Adjourned at 5:10 P.M.

PATRICIA A. BERGERON  
Secretary-Treasurer

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MULTIPLE SMALL BOWEL DIVERTICULA — *Continued from Page 81*

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DISEASE REPORTING IN MAINE: METHOD AND PURPOSE — *Continued from Page 96*

will keep the physicians abreast of changes in the recommendations for immunizations, and in the prevention and treatment of infectious diseases. Information on the national level comes from Center for Disease Control, but of course information from within the State can only come from interested Maine physicians.

5. *Disease Reporting and Other Feedback Help Direct State Funds and Aid Where it is Most Needed.* Public Health nursing programs, venereal disease education for teenagers, school immunization programs and other endeavors are to a large extent based upon expression of need in the medical and lay community. Since those who provide funds often request proof of the need for these programs, the accumulation of morbidity statistics is essential for program planning and evaluation. The Maine State government believes that disease-reporting is important to the health care of citizens, and has enacted legislation (MRSA 22 Section 905) stipulating that physicians shall report "notifiable diseases" to the Bureau of Health. Realizing that a

physician's time is precious, the Bureau has made reporting as simple and practical as possible. For emergency situations, epidemics or advice about infectious diseases, isolation procedures or antibiotics, a phone call serves best. The Bureau's number is 289-3201 in Augusta. At night, the State epidemiologist's number at home should be available (currently 549-3981). For routine reporting, the Bureau has distributed postage-free, self-addressed envelopes with reportable diseases printed on the outside. Only a few minutes are required to fill one out, and the office nurse could do this under the physician's instructions. Mailing the forms entails no cost to physicians and each form contains a place to check if more are needed.

Maine's Bureau of Health is a small, personal body of individuals, in contrast to the situation in many other states. We are interested in and accessible to physicians' problems. Facilitating disease reporting and using data in a fashion which will help Maine citizens is a goal which we hope to share with all physicians in the State.

# The Abdominal Crisis of Hyperlipidemia

STEPHEN A. SOKOL, M.D.

Severe abdominal crises can occur in patients with hyperlipidemia, most commonly in Types I and V (see Table 2) and occasionally in Type IV, if provoked by excess dietary fat or estrogen containing birth control pills. Type I will usually present in infancy "in the first weeks of life when the infant develops colic and a prominent abdomen."<sup>2</sup> These cases are rare. Approximately thirty-five have been found. Type V hyperlipidemia will commonly present as an acute abdomen in the second or third decade. This paper presents three cases of Type V hyperlipidemia, two of which have had repeated episodes of abdominal crises. One patient developed symptoms at the age of seven; the other, although more typical in presentation, underwent laparotomy for acute appendicitis before he was diagnosed.

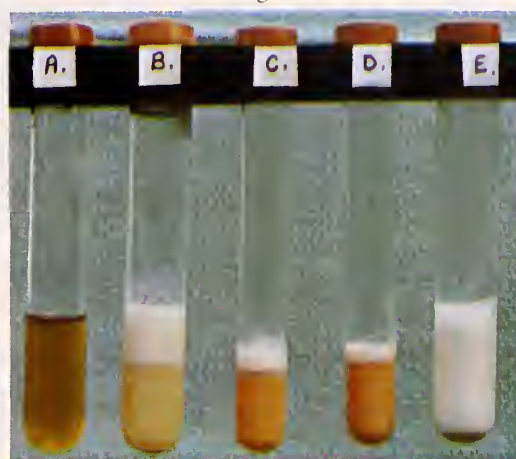
## CASE REPORTS

R.M., a twenty-six year old male, was admitted to the hospital with abdominal pain. He had a history of intermittent abdominal pain for approximately two years which he described as colicky, located in the upper epigastrium and right upper quadrant. It was usually associated with nausea and vomiting and typically occurred once a month. He was unable to relate it to food or to activity. Approximately a year prior to this admission, he was in the hospital because of a similar attack of pain. At that time a diagnosis of acute appendicitis was made and the patient explored. Findings on exploration were a normal appendix and congested lymphatics. Laboratory data from that admission showed triglycerides of 693 mgs% and a urine that contained 300 mgs% of albumin. As an out-patient, he was discovered to have a cholesterol of 196 mgs% and triglycerides of 2,562 mgs%. The triglycerides were repeated on two subsequent occasions and reported as 2,137 mgs% and 2,815 mgs%. His lipoprotein electrophoresis was considered to be either a Type V or a nonfasting Type IV. He was lost to follow-up until the present admission. His symptoms began 48 hours prior to hospitalization when he developed typical attack of abdominal pain which did not clear. Twenty-four hours prior to admission, the pain became intractable. He developed nausea and vomiting, presented to the Emergency Room and was admitted.

Physical examination on admission showed an ill-appearing man lying quietly in bed with a blood pressure of 140/80, pulse, 70 and respirations, 18. *Pertinent findings:* The skin showed no rash. Bowel sounds were present and there was tenderness in right upper quadrant and epigastrium. There was a spleen tip palpable. The remainder of the examination was unremarkable. *Laboratory data:* Initially triglycerides were 900 mgs% with a cholesterol of 185 mgs%. Lipoprotein electrophoresis revealed chylomicrons in a pattern interpreted as nonfasting Type IV or a Type V. Urine amylase was elevated to 2,300 and serum amylases were normal. Urinary protein was initially 4½ grams in 24 hrs. Follow-up urinary protein after the attack showed only 170 mgs. in 24 hrs. Renal function was otherwise normal as were the fasting blood sugar and thyroid function. *Hospital course:* The patient was treated symptomatically as an acute pancreatitis on a basis of hyperlipidemia. His symptoms resolved. He was then begun on oral feedings and was discharged. He has had a recent admission precipitated by a pizza and alcohol.

B.M., the 22-year-old brother of R.M., was seen following a family screen. His history goes back to the age of seven when he began having intermittent attacks of abdominal pain with nausea and vomiting. Examination at that time showed an enlarged

Fig. 1



A. Normal Serum

B. Patient S.S.

C. Patient R.M.

D. Patient B.M.

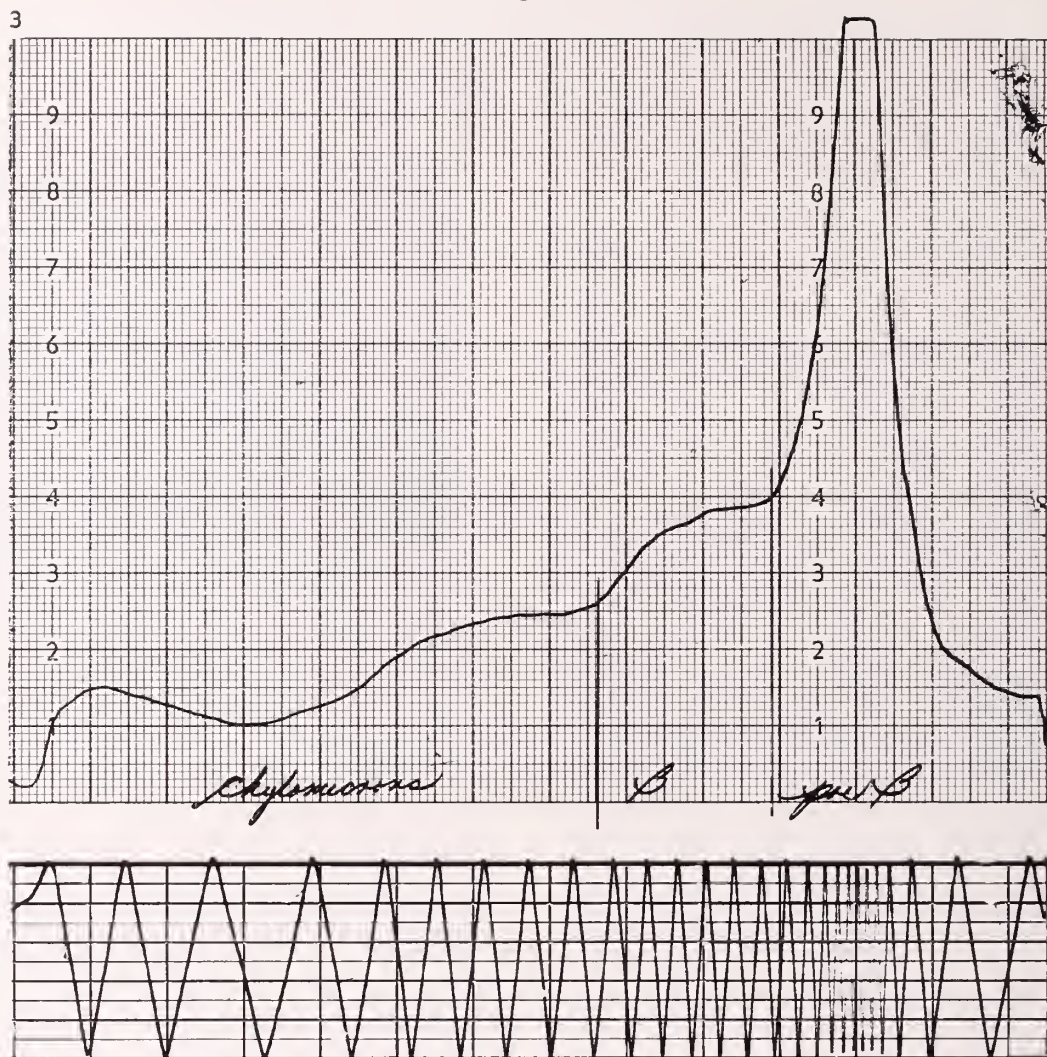
E. Patient B.M. Two hours after a meal. Serum not allowed to settle.

Note creamy layer of chylomicrons  
overlying extremely turbid infranantant

spleen. The patient described these attacks of abdominal as an epigastric aching sensation with some nausea and occasional vomiting. He could not characterize this further nor could he relate it to meals. In 1972, he evidently had a skin eruption, which was treated symptomatically. There has been no recurrence. Physical examination showed a fullness in the left upper quadrant consistent with a spleen tip. *Laboratory data:* Cholesterol was 430 mgs% with triglycerides of 2,538 mgs%. Lipoprotein phenotyping was nonfasting Type IV or Type V. Lipoprotein electrophoresis showed chylomicrons, dense pre and beta functions. Thyroid function, fasting blood sugar and renal function were normal. Urinalysis was unremarkable. *Course:* Patient has been started on appropriate diet and nicotinic acid.

S.S., a 36-year-old man, was discovered to have elevated cholesterol and triglycerides on a routine screen. He has no symptoms referable to this and his physical examination was entirely unremarkable. His cholesterol level was 329 mgs% and triglycerides were 4,000 mgs%. A copy of his lipoprotein electrophoresis (Fig. 2) is included and is consistent with Type V hyperlipidemia. The patient's family is undergoing screening evaluation, and at this time his sister has been found to be a Type IV while his children are normal.

The confusion about lipid disturbances was clarified by the classification of Fredrickson, et al in 1967.<sup>1</sup> Tables 1 and 2 show the major lipoproteins, their characteristics and the classification of these disorders. Chylomicrons are composed mainly of dietary (exogenous) triglycerides. They are formed in the intestinal cell and then are carried via the lymphatics into the blood stream. Most organs clear chylomicrons from the blood stream rapidly and they are not normally detected after an overnight fast. Very low density lipoproteins (VLDL) are synthesized in the liver, and may also be synthesized in the intestine and can mimic chylomicrons. They may represent a continuous spectrum of particles<sup>3</sup>



LIPOPROTEIN ELECTROPHORESIS FROM PATIENT S.S.

Note the large chylomicron band and the marked elevation of the pre beta fraction.

and chylomicrons may become VLDL to some extent after partial removal of triglycerides. While that is speculation, there is no question now that VLDL become low density lipoprotein (LDL) after partial removal of triglyceride and complete removal of a lipoprotein fraction (lipoprotein C).<sup>5</sup>

Type V hyperlipidemia is best comprehended as a mixed type, consisting of Types I and IV. Among eighty-eight parents and siblings of twenty-two patients with familial Type V, 33/88 were normal; 32/88 were Type IV; 23/88 were Type V.<sup>12</sup> The relationship between the two is not understood nor is the mode of inheritance. It is well known that an insulin-dependent diabetic with Type IV hyperlipidemia will often, with worsening of his diabetes, develop a Type V pattern. Thus, these patients may represent a heterogeneous group of metabolic disorders with a common phenotypic expression. The major metabolic impairment appears to be the clearance of dietary fat. Unlike Type I in which there is

an absolute lack of lipoprotein lipase, the enzyme, when measured in Type V, has been in the low normal range. Indeed, postheparin lipolytic activity (PHLA), lipoprotein lipase release following heparin, is one method of distinguishing between Types I and V. It appears at the present that the metabolic pathway for chylomicrons and VLDL is the same — lipoprotein lipase. It is most likely that the disease represents a saturation of this pathway. In other words, the amount of lipoprotein lipase available is not sufficient to clear exogenous and endogenous triglycerides from the circulation. A very good analogy can be made with an insulin-dependent diabetic. As mentioned before, these patients usually have Type IV hyperlipidemia. Insulin activates lipoprotein lipase. In its absence, chylomicrons will appear in great quantity in the serum especially after fat ingestion, converting them to a Type V pattern. It is interesting to note that most patients with Type V hyperlipidemia (approximately 80%) have abnormal

TABLE 1<sup>7</sup>

## CHARACTERISTICS OF FAMILIES OF PLASMA LIPOPROTEINS

	Density (g/cc)*	Electrophoretic Mobility+	Percent Protein (by weight)	Percent of the Total Lipid (by weight) Cholesterol	Triglycerides	Phospholipid
Chylomicrons	<0.95	Remains at origin	1-2	2-12	80-95	3-15
Very low density lipoproteins (VLDL)	0.95-1.006	Pre-beta‡	10	9-24	50-80	10-25
Low density lipoproteins (LDL)	1.006-1.063	Beta‡	25	57	13	30
High density lipoproteins (HDL)	1.063-1.210	Alpha‡	50	30	10	60

\*Used to separate and classify lipoproteins in the preparative or analytical ultracentrifuges.

+On paper or agarose gel.

‡As compared to the globulins.

<1.006 g/cc.

TABLE 2<sup>7</sup>

## LABORATORY AND BIOCHEMICAL CHARACTERISTICS OF THE HYPERLIPOPROTEINEMIAS\*

Phenotype	Definition	Plasma Cholesterol	Plasma Triglycerides	Electrophoresis Pattern	Plasma Appearance, 12 hours at 4°
I	Chylomicrons present; Absence of adipose tissue lipoprotein lipase	Normal or increased	Increased	Chylomicrons present	Creamy layer with clear infranatant
IIa	LDL increased	Increased	Normal	Increased beta lipoproteins	Clear
IIb	Increased LDL and VLDL	Increased	Increased	Increased beta and pre-beta lipoproteins	Uniform turbidity
III	Floating beta-lipoprotein present+	Increased	Increased	Broad beta-lipoprotein band present, extending into pre-beta region	Uniform turbidity a creamy layer may also be present
IV	Increased VLDL	Normal or increased	Increased	Increased pre-beta lipoproteins	Uniform turbidity
V	Chylomicrons present; increased LDL, adipose tissue lipoprotein lipase	Normal or increased	Increased	Chylomicrons present, pre-beta lipoproteins	Creamy layer with turbid infranatant

\*These findings applied to the untreated hyperlipoproteinemia.

+ Floating beta-lipoprotein is an abnormal lipoprotein, with beta electrophoretic mobility, present in the plasma fraction of density

glucose tolerance tests and the majority have hyperinsulinemia.<sup>3</sup> These facts suggest that PHLA may be limited or may be abnormal in type. One subject has been studied whose PHLA failed to hydrolyze chylomicrons although it was active against coconut oil. It has also been observed that women with Type IV hyperlipidemia will often decompensate into a Type V hyperlipidemia with marked elevation in triglycerides when given estrogen containing medication. Estrogen depresses lipoprotein lipase (PHLA).

Before a diagnosis of Type V hyperlipidemia can be made, the pseudohyperlipidemias must be excluded. As alluded to above, other metabolic conditions can mimic a Type V pattern. Most common are insulin-dependent diabetes mellitus, pancreatitis, alcoholism, nephrosis and hypothyroidism. Less common causes are estrogen compounds given to a Type IV patient, dysgammaglobulinemia, glycogen storage disease, Werner's syndrome, idiopathic hypercalcemia and lipoatrophic diabetes mellitus. Most likely the common defect in these conditions is a suppression and/or a

lack of stimulation of lipoprotein lipase (PHLA).

The patients described in this paper present many typical features of the disease as well as unusual ones. The attacks of abdominal pain are most likely secondary to pancreatitis and will usually be observed when the serum triglycerides are around 2,000 mgs%. The diagnosis of pancreatitis is often obscured as hyperlipidemia will interfere with the measurement of lipase and amylase in the serum.<sup>6</sup> It can be detected by urinary amylase concentration or by the amylase/creatinine clearance ratio.<sup>6</sup> Our patient had an elevated urine amylase. Atypical features include the early appearance of the disease in B.M. Records document the onset of his disease at age seven at which time attacks of abdominal pain as well as splenomegaly were observed. The lack of xanthoma in these patients is somewhat atypical in view of their marked elevation of triglycerides, although B.M. did have an undescribed skin rash approximately four years ago. Eruptive xanthoma usually appear when serum triglycerides are approximately 1,500 mgs%. A feature that has never been described before is the appearance of significant

proteinuria in R.M. during his attacks of abdominal pain. Although total urinary protein during and after the attack were only measured on this admission, a previous urinalysis during an attack showed 300 mgs% of protein. It is suggested that this represents transient ischemic damage to the kidney and that the attacks of the abdominal pain, pancreatitis, are on a similar basis. Other organ dysfunction has been noted in hyperlipidemia. Kuo and Joyner,<sup>10</sup> in 1957, were able to induce angina in patients with ischemic heart disease by feeding them fat and claimed that clearing of the lipemia by heparin relieved the pain immediately. Heilman and Fisher<sup>11</sup> presented a patient who would develop dementia every time her triglycerides became markedly elevated. They suggested that it might be secondary to decreased blood flow because of the known effects of triglycerides to increase coagulability and to increase red cell agglutination. Havel suggested that ischemia could result from clumping of chylomicrons interfering with blood flow. Regardless of the mechanism, it seems clear that marked elevation of triglycerides either endogenous (Type IV) or exogenous (Type V) will cause organ dysfunction on an ischemic basis.

The treatment of the hyperlipidemia consists primarily of diet. Drugs are added depending on the severity of the lipemic process and/or on response to diet therapy. Dietary manipulation in Type V reduces the intake of fat to 25 to 30% of total calorie intake. Calories are restricted to obtain ideal weight. As VLDL will increase markedly on a high carbohydrate intake, these are restricted, mainly sucrose and fructose. These are the greatest inducers of VLDL synthesis by the liver. Alcohol for the same reason is avoided.

The drug of choice in Type V hyperlipidemia is nicotinic acid. This decreases VLDL synthesis in

the liver by inhibiting lipolysis in fatty tissue.<sup>2,3,7</sup> Side effects include nausea, gastric irritation, flushing, increased pigmentation, abnormal liver function tests and worsening of glucose tolerance. The maximum daily dose is 3 grams. More than that will only increase side effects without increasing efficacy.

For patients who cannot tolerate nicotinic acid, progesterone<sup>9</sup> in females and anabolic steroids<sup>8</sup> in males have been used with excellent results. The action is thought to be related to an enhancement of peripheral lipolysis via lipoprotein lipase.<sup>8</sup>

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#### EVERY MAN'S GUIDE TO THE TREATMENT OF DIABETIC RETINOPATHY

*Continued from Page 92*

tachment occurs. Checking the patient's vision on each examination, dilating the pupil and searching for evidence of retinopathy, and recording intraocular pressures with a tonometer (diabetics have a significantly higher incidence of glaucoma than the average individual), are the basic commitments that the primary care physician must make if he wishes to assume the role of monitoring the patient's ocular aspects of his disease. Those who choose to concern themselves with the general medical management of diabetes should insure that the patient is followed annually by an ophthalmologist from the time that the patient is first diagnosed as having diabetes to insure therapy being offered when necessary at the earliest appropriate time. Vision, thereby, will to a large extent be preserved and many needless cases of blindness will be prevented.

In summary, while the primary care physician still has many significant problems associated with the management of his diabetic patient, he has grounds

for optimism in regard to the ocular aspects of this disease. Photocoagulation techniques, such as those performed with a laser, offer a documented effective approach to significantly reducing the incidence of visual loss secondary to diabetic retinopathy.

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TABLE 3

DOUBLE-BLIND CLINICAL STUDIES OF PROPOXYPHENE MIXTURES

Reference	Drug <sup>a</sup> and Strength (mg)	Placebo Control ?	No. of Patients (or trials)	Type of Pain	Frequency of Administration	Frequency of Efficacy Measurements	Conclusions on Efficacy
1 36	PRX HCl (65) [as loose powder] + APC PRX HCl (65) [as spherule] + APC PRX HCl (65) [as loose powder] + ASP (325) PRX HCl (65) [as spherule] + ASP (325)	Yes	432	Postpartum	Single dose	1,2,3,4,6 hrs (by observer)	No difference between combinations. All combinations superior to placebo.
2 37	ASP (227) + PHEN (160) APC PRX Nap (100) + APC ASP (454) PHEN (320) ASP (454) + PHEN (320) ASP (454) + PHEN (320) + Caffeine (60) PRX Nap (200) + ASP (454) + PHEN (320) + Caffeine (60) ASP (908) PHEN (640)	No	610	Postpartum		1,2,3,4,6,8 hrs (by observer)	No difference between high low-dose preparations. Preparations with PRX Nap provided greater analgesia; no difference between other preparations.
3 38	PRX HCl (65), ASP (227), PHEN (162), Caffeine (32) [1 capsule of Darvon Compound-65] Butalbital (100), ASP (400), PHEN (130), Caffeine (80) [2 capsules of Fiorinal]	No	200	Postpartum	Single dose	1,2,3,4 hours (by observer)	No difference between preparations.
4 25	(See study number 4 in Table 1)						
5 39	COD (32) + APC PRX HCl (32) + APC COD (32), ASP (162), PHEN (192), Phenobarbital (16), Hyoscyamine (0.031) PRX HCl (32), ASP (162), PHEN (192), Phenobarbital (16), Hyoscyamine (0.031)	Yes	312	Dental	Single dose	Once at a specified time (by patient)	?
6 26	(See study number 5 in Table 1)						
7 40	COD (16) + ASP (1000) PRX HCl (65) + ACET (650) PTZ (50)	Yes	53	Cancer	Single dose	1,2,3,4 hours (by observer)	COD + ASP superior to PRX + ACET. PRX + ACET superior to PTZ. All drugs superior to placebo.
8 41	PRX HCl (65) + ACET (650) PTZ (30) + ACET (1000)	No	62	Arthritis	4 times daily	1 week (by observer)	PTZ + ACET preferred to PRX + ACET.
9 42	ASP (500) ASP (500) + PRX Nap (50)	No	45	Arthritis	3 times a day	Not stated (by patient)	No difference between drugs.
10 43	COD (65) + ASP (650) PTZ (25) + ASP (650) Oxycodone (9) + ASP (650) PRX Nap (100) + ASP (650) ETHO (75) + ASP (650) PROM (25) + ASP (650) Pentobarbital (32) + ASP (650) Caffeine (65) + ASP (650) ASP (650)	Yes	100	Cancer	Single dose	Variable (by patient)	COD + ASP, PTZ + ASP, and oxycodone + ASP provided greater pain relief than ASP alone. PRX Nap + ASP, ETHO + ASP, PROM + ASP, Pentobarbital + ASP, and Caffeine + ASP provided no more relief than ASP alone. All drugs superior to placebo.
11 34	(See study number 13 in Table 1)						

<sup>a</sup>For drug abbreviations, see footnote to Table 1.

tigo, light-headedness, drowsiness, headache, etc.), and rash.

The frequency and character of adverse effects in ambulatory patients are not entirely clear since few

studies have specifically addressed this question. In an investigation of PRX HCl, PRX Nap, and placebo in 120 healthy prisoners, no differences were observed between drugs and placebo in the

frequency of subjective symptoms, hematologic response, blood chemistry, urine analysis, and routine physical examination.<sup>48</sup> The dose of PRX HCl was 65 mg, four times daily, and that of PRX Nap, 100 mg four times daily. Data were collected two weeks prior to the study, at the beginning of the study, and at 2, 4, 8, 12, 16, 21, and 26 weeks during the study.

Other than the minor adverse effects described above, some rare untoward events have been reported. In two separate case reports, PRX HCl has been implicated as a cause of hepatotoxicity.<sup>49,50</sup> The patients were taking PRX preparations for headache or sciatic pain when they experienced dark urine, jaundice, and other symptoms of hepatotoxicity. When examined, they were found to have elevated liver function tests; one patient had an abnormal liver biopsy. All symptoms cleared within several days when PRX was discontinued, and laboratory values eventually returned to normal. Seven weeks to two years after the initial episodes, the patients again took PRX and within 24 hours they had the same symptoms. This rare effect of PRX probably represents a hypersensitivity reaction.

Recurrent episodes of hypoglycemia in a patient with renal disease and metastatic carcinoma have been reported.<sup>51</sup> When the patient fasted without taking PRX, no significant hypoglycemia was observed, but when she fasted after taking PRX on the previous evening, cerebral symptoms and hypoglycemia occurred.

In usual therapeutic doses PRX does not cause measurable respiratory depression. In a study of 12 volunteers, 180 mg of PRX were needed to produce a degree of respiratory depression equivalent to 60 mg of codeine.<sup>52</sup> Thus, PRX appears to be about one-third as potent as codeine as a respiratory depressant.

Congenital malformations have not been associated with the use of PRX, even in high doses. One case of malformations in the offspring of a mother who had taken large amounts of PRX and numerous other drugs has been reported; however, no causal association could be established.<sup>53</sup> Experiments in rats and rabbits with high doses of PRX Nap did not reveal any sign of drug-induced teratogenicity.<sup>54</sup>

PRX has no effect on bleeding time or platelet aggregation.<sup>55</sup>

In a double-blind, placebo-controlled investigation of the effects of alcohol, 15 ml per 50 lb body weight, and PRX HCl 65 mg on 17 tests of performance in eight volunteers, alcohol had a greater effect than PRX.<sup>56</sup> PRX produced only slight decrements in motor coordination, mental performance, and stability of stance. The combined effects of the two drugs were no greater than would be predicted from the simple sum of the two effects, and in some instances they were less than expected.

In summary, the adverse effects of PRX when taken in usual therapeutic doses are few and mostly minor. In comparison to many other mild

analgesics, PRX has a remarkably low propensity to cause side effects.<sup>47</sup>

## OVERDOSAGE

### *Frequency*

Table 4 lists published reports of accidental and intentional overdoses of PRX alone and in combination with other drugs. It does not include patients with no major symptoms of toxicity, patients who were not hospitalized, overdoses stemming from abuse, and reports in which few details were given. The published reports undoubtedly represent only a fraction of the overdose cases that have actually occurred.<sup>76</sup>

Serious toxicity due to PRX overdosage was reported infrequently in the 1960's, and it was widely assumed that PRX was a relatively innocuous drug. However, in the early 1970's many reports of serious toxicity were published, and in 1975 and 1976 two reports were published showing that PRX-related deaths were increasing.<sup>87,88</sup> Most of the deaths apparently stem from intentional overdoses of PRX, often in combination with other drugs (including alcohol). However, overdosage due to accidental ingestions is also a substantial problem.<sup>89</sup> The gravity of overdosage symptoms is so serious that PRX intoxication must be considered a major public health problem.

### *Clinical Presentation*

The most frequently reported major symptoms of PRX overdosage are coma, convulsions, and respiratory depression. Nausea, vomiting, drowsiness, and other relatively minor symptoms occur as early as 30 minutes after ingestion. The onset of coma, convulsions, and respiratory depression is usually about one hour after ingestion, regardless of the size of the dose. The duration of coma and apnea is usually longer in those ingesting larger quantities. Patients who do not have convulsions usually have involuntary movements. Respiratory depression often progresses to apnea; cyanosis and other signs of hypoxia are common. Irreversible anoxic brain damage may occur<sup>62</sup> even though the patient may be resuscitated.<sup>67,75</sup> Pulmonary congestion, edema, and hemorrhage have been reported in some patients;<sup>67,69</sup> they are a common and nonspecific autopsy finding in fatal overdose cases and appear to be a consequence of respiratory depression and seizures. Hypotension occurs frequently; the pulse may be absent and a blood pressure reading may be unobtainable. In severe intoxications, cardiac arrest and cardiovascular collapse may occur.<sup>62,71</sup> Electrocardiographic abnormalities include transient right heart block,<sup>63</sup> bigeminy,<sup>62</sup> prolongation of the QRS complex associated with ST-T wave changes,<sup>67</sup> and other disturbances.

Children and adults do not appear to differ appreciably in the toxicity usually observed; children may be more prone to convulsions and, of course, may require smaller doses for a toxic effect.

TABLE 4

## PUBLISHED REPORTS OF PROPOXYPHENE OVERDOSAGE

Author(s)	Reference	Year of Publication	Ingestions of Propoxyphene Alone		Ingestions of Propoxyphene with Other Drugs		
			Nonfatal Cases	Fatal Cases	Other Drugs	Nonfatal Cases	Fatal Cases
Cann, et al	57	1960	3	0	APC <sup>a</sup> (Darvon Compound)	3	0
Hyatt	58	1962	1	0	—	0	0
Storts	59	1963	0	0	?	1	0
Frasier, et al	60	1963	1	1	—	0	0
Swarts	61	1964	1	0	—	0	0
McCarthy, et al	62	1964	0	1	—	0	0
Qureshi	63	1964	1	0	—	0	0
Hara	64	1964	0	0	APC (Darvon Compound)	1	0
Cawood, et al	65	1966	1	0	—	0	0
Karliner	66	1967	0	1	—	0	0
Gary, et al	67	1968	0	1	—	0	0
Billig	68	1968	1	0	—	0	0
Bogartz, et al	69	1971	1	2	—	0	0
Worm	70	1971	0	3	?	0	2
Sigurd, et al	71	1971	1	0	—	0	0
Kaufman, et al	72	1972	0	0	paramethasone and aspirin (Stero-Darvon <sup>®</sup> with A.S.A. <sup>®</sup> )	1	0
Young	73	1972	1	5	APC (Darvon Compound)	0	2
					Salicylate, possibly others	0	2
Feinberg	74	1973	1	1	—	0	0
Zavelson, et al	75	1973	1	0	—	0	0
Sturner, et al	76	1973	0	10	Alcohol	0	12
					Dimenhydrinate	0	1
					Chlordiazepoxide	0	1
Rios	77	1973	0	1	Salicylate	0	1
Kersh, et al	78	1973	1	0	Diazepam	1	0
Hunt	79	1973	0	0	Acetaminophen (Distalgesic)	1	0
Tarala, et al	80	1973	0	0	Acetaminophen (Distalgesic)	1	0
Warren, et al	81	1974	0	0	Aspirin (Darvon-N with A.S.A.)	0	1
Sundkvist, et al	82	1974	0	0	Various drugs	0	63
Cravey, et al	83	1974	0	5	Alcohol	0	2
					Barbiturates	0	2
Vlasses, et al	84	1974	2	0	—	0	0
Lovejoy, et al	85	1974	1	0	—	0	0
Mauer, et al	86	1975	0	1	—	0	0

<sup>a</sup>APC is aspirin, phenacetin, and caffeine

Lethal doses and blood levels of PRX have varied considerably in published reports.<sup>67,68,70,74,90</sup> However, on the basis of extensive experience with fatalities due to PRX overdoses, McBay and Hudson have concluded that only 15 to 20 of the 65 mg PRX HCl capsules or 100 mg PRX Nap tablets may cause death, and that lesser amounts may be fatal with ethanol or other central nervous system depressants.<sup>87</sup> Survival depends not only on the size of the dose but upon the rapidity of absorption and timing and efficacy of resuscitative measures.

Toxic effects may develop more slowly with the napsylate salt because of slower absorption but, despite claims to the contrary,<sup>91</sup> there is no evidence that the napsylate is safer than the hydrochloride. Alcohol apparently renders overdoses of PRX more lethal than overdoses of PRX alone;<sup>92</sup> this is probably due to a simple additive effect.

### Treatment

Activated charcoal has been shown to adsorb PRX in vitro<sup>93</sup> and in vivo in dogs<sup>94</sup> and human volunteers.<sup>95</sup> In the latter study plasma levels of

PRX were compared in a crossover study of six males. Plasma levels were more than twice as high when PRX was administered alone as when given with charcoal. Approximately 80 mg of a 130 mg dose of PRX was adsorbed by 4 g of charcoal. Charcoal may be a less effective adsorbent when given after PRX ingestion.

Naloxone has satisfactorily reversed all symptoms of PRX intoxication in the four published accounts of its use.<sup>78,80,84,85</sup> In using naloxone the goal is to achieve a distribution of the antagonist that is sufficient to displace the intoxicating narcotic from its attachment to the patient's narcotic receptors. The beneficial effects of naloxone will continue only if sufficient levels of the antagonist are maintained relative to the amount of PRX present.<sup>96</sup> Since naloxone is metabolized more rapidly than PRX, naloxone concentrations may fall to subtherapeutic levels while PRX concentrations still remain at toxic levels. Thus, life-threatening symptoms of PRX intoxication may recur within minutes of naloxone dosage. Since symptoms of PRX intoxication usually last for 8 to 12 hours, the requirement for

additional naloxone should be determined by continued monitoring of pulse, respiratory rate, mental status, and pupillary size. Naloxone should be given intravenously.

Prior to the availability of naloxone, nalorphine and levallorphan, two other narcotic antagonists, were used in PRX intoxication. These agents are no longer recommended because they have intrinsic respiratory and cardiovascular depressant effects.<sup>78,80</sup>

Some clinicians have expressed reservations about the efficacy of narcotic antagonists in PRX intoxication because of the apparent failure of these agents to reverse symptoms in some cases. However, in all of the reported failures it appears that either insufficient doses of nalorphine were given or the antagonist was given after anoxic brain damage may have occurred.<sup>62,66,69,75,86</sup> In a large number of other published reports nalorphine did reverse the symptoms of PRX intoxication.<sup>60,61,63,65-68,72,73,79</sup>

Except for one or two anecdotal reports,<sup>97</sup> naloxone has no known acute adverse effects. Thus, there appears to be no contraindication to its early and frequent use. Since naloxone does not depress respiration, it can be used in a therapeutic trial when the nature of the intoxicant is uncertain or in a situation in which drowsiness occurs in combination with respiratory depression due to another drug.

Peritoneal and hemodialysis have been used in an attempt to remove PRX, but in all reported cases it was unsuccessful.<sup>62,66,67,86</sup> These failures stem from its large apparent volume of distribution.

Forced diuresis is of little benefit because renal clearance of unchanged PRX contributes very little to its total metabolic clearance.

## DEPENDENCE AND ABUSE

### *Dependence*

Published reports on dependence to PRX may be divided into two major groups: reports of experiments conducted under carefully controlled conditions and case reports of dependence arising from illicit use.

The experimental studies have used a variety of methods to evaluate the dependence potential of PRX. The technique that is most relevant to clinical use involves administration of PRX in its recommended therapeutic dose over a moderately long period of time. Then a narcotic antagonist is given or the drug is abruptly withdrawn to determine if physical dependence has developed. In one double-blind study using this methodology, 12 subjects were given PRX 65 mg four times daily for six months and then given nalorphine 3 mg intramuscularly.<sup>98</sup> No evidence of physical withdrawal symptoms was observed in any of the patients. In a similar study, 19 patients were given PRX 65 mg four times daily for three months and then abruptly withdrawn.<sup>99</sup> Three of the patients exhibited minor abstinence symptoms (eg, nausea, diarrhea). Nalorphine was also given at two-week intervals during the study. Some

minor withdrawal symptoms were provoked by the antagonist, but they were not considered clinically significant.

A similar type of experiment involves administration of high doses of analgesic. In a study in former addicts<sup>100</sup> the dose of PRX was increased as rapidly as possible during an 18-day preliminary period in five subjects; the maximum daily dose was 825 mg. This dosage was maintained for 53 or 54 days, then abruptly discontinued. All of the subjects had subjective complaints and objective signs of mild physical abstinence (eg, yawning, perspiration). Nalorphine was also given at 30 to 40 days, and it provoked slight signs of abstinence in two of the five subjects.

Other assays of the dependence liability of PRX have been done. Single doses of PRX (50 to 60 mg orally or 5 to 250 mg subcutaneously) have been administered to former addicts.<sup>100</sup> At oral doses above 355 mg some pleasant subjective effects were reported, but a full pattern of morphine-like subjective effects or behavioral changes was not observed in any of the addicts. PRX has been substituted for morphine for 24 hours and 14 days in morphine addicts; it only partially suppressed physical abstinence symptoms. Codeine, by comparison, suppressed abstinence symptoms very well.<sup>100</sup> PRX, codeine, and morphine have been included in dependence studies of two investigational analgesic drugs, and in both instances PRX was substantially less addictive than morphine or codeine.<sup>101,102</sup>

Following the publication of the dependence experiments in the early 1960's, case reports of dependence to PRX began to appear.<sup>103-108</sup> In general, these reports seem to verify the earlier studies since relatively few documented cases of physical dependence have been reported. Physical dependence to orally administered PRX with signs and symptoms of abstinence, has been well documented in only two case reports;<sup>103,104</sup> these cases took high doses (1900 to 2300 mg daily) orally for long periods. Parenteral abuse can lead relatively quickly to mild physical dependence, but the addiction cannot be sustained because of rapid development of tolerance and deleterious effects on soft tissues and veins at the site of injection.<sup>109</sup>

In other reports, tolerance to the depressant effects of high doses of PRX and psychic dependence have been noted; minor withdrawal symptoms have been reported in some cases. Neonatal withdrawal symptoms associated with maternal use of PRX have been reported.<sup>110,111</sup>

### *Abuse and Misuse*

In contrast to its limited dependence liability, PRX's abuse potential appears to be substantial. Large numbers of civilians and military personnel have used high doses of PRX for its pleasurable subjective properties.<sup>112-118</sup> Indeed, it appears that PRX is one of the most popular drugs of abuse. Undoubtedly, abuse is abetted by the widespread

availability of PRX.

PRX is also misused by many persons who have no abuse intentions. For example, some patients take higher than normal doses in an effort to achieve greater pain relief; in some cases, overdosage symptoms may occur. If patients are also taking other drugs that depress the central nervous system, they are even more prone to develop symptoms of overdosage.

The most common form of PRX abuse appears to be occasional oral use for obtaining a "high". Apparently, few chronic drug abusers use PRX in preference to other drugs on a continuous basis.<sup>114</sup> The most frequent regular chronic abuse of PRX probably occurs among opiate addicts when the opiate of preference is in short supply or when the addict has been jailed or hospitalized.<sup>114</sup> Since most opiate addicts abuse narcotics by the intravenous route, they also abuse PRX by this route. Opiate addicts return to their drug of preference as soon as possible because PRX does not provide the same degree of euphoria and produces severe damage to veins.

PRX is also abused in combination with other drugs (eg: meprobamate, barbiturates, glutethimide),<sup>88,114</sup> and in some cases, these combinations are used by former opiate addicts who have decided to escape the "strung-out" feeling and expense of opiate addiction.<sup>119</sup> Some opiate addicts use PRX as a drug for self-treatment of their addiction.<sup>114,120</sup>

Abusers who prefer to administer PRX subcutaneously or intravenously commonly obtain a PRX compound product which contains a pellet of PRX HCl inside each capsule (eg, SK-65 Compound). The pellet is crushed, mixed with a small amount of water, then injected. Darvon Compound-65, the original PRX compound product, no longer contains a pellet; the PRX is uniformly dispersed throughout the other ingredients and filler in the capsule. However, the presence of other active ingredients probably does not constitute a significant barrier to abuse since they have little effect when injected. PRX HCl or Nap is easily isolated from those dosage forms containing no other active ingredients by dissolving a tablet or the contents of a capsule in warm water and filtering.

Although there have been no reports of abuse of the relatively recently marketed napsylate salt, it may have the same abuse potential.

The Drug Enforcement Administration of the Department of Justice has recently moved to classify PRX as a schedule 4 controlled substance; this action limits the number of refills to five in a six-month period. Over the past 15 years stricter controls have been advocated by the World Health Organization, the Drug Enforcement Administration itself, and most recently, the Food and Drug Administration and Department of Health, Education, and Welfare. HEW agreement is needed for the Justice Department unit to act.

#### *Adverse Effects Associated with Abuse*

Local complications at the injection site are prob-

ably the most commonly reported adverse effect of PRX abuse. Abscesses, cellulitis, thrombophlebitis, and sclerosis of veins occur after 6 to 12 weeks of parenteral abuse,<sup>121,122</sup> even if sterile techniques have been used.<sup>109</sup> Intravenous abuse has also been associated with foreign body granulomata and angiomatoids in the pulmonary arterioles<sup>123</sup> and disseminated intravascular coagulation, intravascular hemolysis, and acute renal failure.<sup>120</sup> Like many other drugs, PRX causes ischemic changes, and occasionally necrosis or gangrene, when it is accidentally injected intra-arterially.<sup>124</sup>

Psychotic reactions have been reported in casual abusers. Delusions, hallucinations, disorientation, and extreme confusion were the principal clinical manifestations. After discontinuation of PRX, psychotic symptoms resolve within three to five days.

In cases where very high doses of PRX have been used, the clinical picture resembles that of an acute intoxication (see above). Deaths have been reported.<sup>109,115,116</sup>

#### COMMENT

It is now more doubtful than ever that PRX HCl 65 mg provides an analgesic effect equal to that of aspirin 650 mg. The introduction of the napsylate salt of PRX has not provided a more effective preparation, and the napsylate has no other clinically significant advantages over the hydrochloride. There is no conclusive evidence that combinations of PRX with other analgesics are more effective than PRX or other analgesics alone. In view of these findings, the continued widespread use of PRX preparations is perplexing. This popularity is even more idiosyncratic now in view of the serious problems of overdosage and abuse that have become evident over the past six years. Continued prescribing of PRX preparations should be carefully reviewed by all physicians who frequently prescribe these drug products.

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## MECO — MEDICAL STUDENT AND PHYSICIAN INVOLVEMENT

MECO (Medical Education & Community Orientation) is a nationally coordinated network of educational programs for pre-clinical medical students, sponsored by the American Medical Student Association. Based in a community hospital or group practice clinic, the summer preceptorship programs offer the student an exposure to the community and to the community health system. Programs include rotation through both clinical and non-clinical areas of the hospital or clinic, observation and participation in physicians' offices, and study of the function of health-related agencies and institutions in the community. The project emphasizes a study of patient-oriented health care and the relationship of the patient to the total health system.

A primary objective of MECO is to effect a redistribution of physician manpower in this country by exposing the student, at an early point in his/her training, to the health care system of the community. In the standard medical school curriculum, a student is exposed only to the specialty-oriented urban and university teaching centers. The MECO project is based upon the premise that there also are valid and worthwhile educational health care institutions in the community, utilizing community physicians. A second long-range objective of MECO is to develop a mechanism to facilitate continuing education of the practicing physician (members of the American Academy of Family Physicians may earn up to 30 hours of continuing education credit through their participation in the MECO project).

Programs may vary from 4-10 weeks but the usual preceptorship is an 8-week period. Participating hospitals and clinics will be asked to provide a weekly stipend (maximum \$85) for each student plus room and board or additional stipends for such expenses where not provided.

### Your participation in the MECO project:

- Introduces the student to the community and to the cultural, economic, political and environmental determinants of health in that community.
- Introduces the student to the organization and operation of health care institutions as related to the delivery of health care in the community.
- Enables students to evaluate their career goals and better plan their medical education as related to specific community needs in health care.

- Provides community exposure to future health care personnel.
- Enables the student to understand the basic concept of patient-oriented health care.

If you are interested in learning more about the MECO project, please return the following questionnaire.

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Mail To: Paul Neustein, MECO coordinator 124 A Oxford Street #9 Cambridge, MA 02140	
Yes, I plan to offer a clerkship and have supplied the information below. Please send the additional information.	
I am still undecided: please send the following additional information: _____	
I am unable to offer a clerkship this year, but please contact me in the future. _____	
Physician/Hospital in charge of clerkship: _____	
Address: _____ Tel: (    ) _____	
Physician Specialty: _____	
Hospital Affiliations: _____	
How many students would you like to take? _____	
Can you provide room and board provisions for the students? _____	
Amount of weekly stipend: _____	
Can you take the student(s) for the usual 8-week period? _____	
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# Necrologies

## WALTON P. C. CLASON, M.D.

1928-1976

Dr. Walton P. C. Clason, 47, of Ellsworth, Maine, died on May 20, 1976.

He was born in Athens, Georgia on July 2, 1928, son of Dr. Freeman P. and Helen C. Clason.

A graduate of Princeton University, he received his medical degree from Harvard Medical School in 1954. Dr. Clason served a rotating internship at the Hartford Hospital in Connecticut and a residency in medicine there. From 1956 to 1958, he served in the U.S. Army Reserves as a Captain in the Medical Corps.

Dr. Clason practiced in Hartford until 1966, when he located in Ellsworth, specializing in internal medicine and cardiology at the Maine Coast Memorial Hospital. He was also Director of the Cardiovascular Section and Medical Director of the Special Care Unit at the Eastern Maine Medical Center, and helped develop the data-phone electrocardiogram transmission system between the Eastern Maine Medical Center and Blue Hill Memorial Hospital, a vital link between expensive city equipment and expertise and the rural patient.

He was a member of the Hancock County Medical Society, the Maine Medical Association and the American Medical Association. He was also a Diplomat of the American Board of Internal Medicine, and a lecturer in Electrical Engineering at the University of Maine at Orono from 1972 until 1976.

Surviving are his widow, Sally Clason of Ellsworth; one son, W. Page C. Clason, Jr. of Ellsworth; three daughters, Mrs. Richard Tibbetts of Albuquerque, New Mexico, Susan G. and Linda C. Clason, both of Ellsworth; and his father and mother of Hartford, Connecticut.

## THEODORE S. HSU, M.D.

1907-1976

Dr. Theodore S. Hsu, 68, of Ellsworth, Maine, died at a hospital in Davis, California on September 9, 1976 after a long illness. He had lived and practiced as an ophthalmologist in Ellsworth and surrounding communities from 1956 until the spring of 1975, when illness forced his retirement.

Born in Foochow, China on October 1, 1907, the son of Weng Ming and Mary Chi-Hwa Hsu, Dr. Hsu came to the United States in 1926 to continue his education. He was graduated from the University of Pennsylvania and received his medical degree from the University of Pennsylvania School of Medicine in 1933. Dr. Hsu interned at St. Luke's Hospital in Bethlehem, Pennsylvania and served a residency at the Graduate Hospital of the University of Pennsylvania. He practiced in China for many years and in Stroudsburg, Pennsylvania, locating in Ellsworth in 1956.

He was an affiliate member of the Hancock County Medical Society and the Maine Medical Association.

Surviving are his widow, Dr. June Hsu of Davis, California; a daughter, Mrs. Donald Post, formerly of Ellsworth, and one granddaughter, Karen Post, both of Newport, North Carolina and several nieces and nephews.

## ONEY P. SMITH, M.D.

1926-1976

Dr. Oney P. Smith, 50, of Wells, Maine, died on December 25, 1976.

He was born in Troy, New York on November 29, 1926, son of Oney P. and Marie J. Smith.

Dr. Smith was graduated from the University of Vermont and received his medical degree from the University of Vermont College of Medicine in 1953. He served an internship at the Providence Hospital in Detroit, Michigan. A family practitioner,

he practiced in Troy, New York and located in Wells in 1960.

He was a member of the York County Medical Society, the Maine Medical Association and the American Medical Association. He was also a member of the American Academy of Family Practitioners, and had served in the U.S. Navy during World War II.

Surviving are his mother of Troy, New York; his widow, Lucille T. Smith of Wells; three sons, Oney P. Smith, Jr. and Gregory S. Smith, both of Wells and Lucas M. Smith of Ogunquit; two daughters, Miss Sharon M. Smith and Miss Tracey L. Smith, both of Wells; and a sister, Mrs. Harry Linin of Albany, New York.

## OSCAR R. JOHNSON, M.D.

1895-1976

Dr. Oscar R. Johnson, 81, of Portland, Maine, died on December 26, 1976 at a local nursing home.

*Continued on Page 112*

### CORRECTION

**Photograph Turned.** — In the article, "Alternate Exposure, Biplane, Magnification Angiography: A Modern Neuroangiographic System," published in the Jan. 1977 issue (68:13-17, 1977), Fig. 1B on page 14 was turned 180°. The correct figure is printed below:



Fig. 1B

Lateral View External Carotid Arteriogram. The middle meningeal artery is greatly enlarged (arrowheads) and tumor vascularity is apparent (arrows). NOTE normal maxillary artery (open arrowhead) and superficial temporal artery (large arrow).

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Born in Monson, Maine on May 7, 1895, he was the son of John L. and Nellie Johnson.

Dr. Johnson was graduated from the University of Maine and received his medical degree from Yale University School of Medicine in 1926. He interned at the Maine General Hospital and served a residency in dermatology at the Massachusetts General Hospital. He started his practice in Westbrook in 1927 and located in Portland in 1931 where he was affiliated with the Children's Hospital, the Maine Eye and Ear Infirmary and the Maine Medical Center until his retirement.

An honorary member of the Cumberland County Medical Society and the Maine Medical Association, he received a 50-year pin in June 1976. He was also a member of the American Medical Association, the New England Dermatology Society, and was a charter member of the American Academy of Dermatology.

Surviving are his widow, the former Mildred M. Shea; two sons, Robert R. of Portland and Warren R. of Wilmington, Delaware; a sister, Esther Pennington of Monson; three grandchildren, and several nieces and nephews.

## CHARLES W. KINGHORN, M.D.

1886-1976

Dr. Charles W. Kinghorn, 90, of Kittery, Maine, died in a New York hospital on December 28, 1976.

He was born in Yarmouth, Maine on September 1, 1886, son of John Wesley and Mary Jane Kinghorn.

Dr. Kinghorn attended the University of Maine and received his medical degree from Bowdoin Medical School in 1915. He interned at the Worcester City Hospital and took postgraduate courses at the Chicago Eye, Ear, Nose and Throat Hospital. He also studied at the University of Vienna in Austria.

He was a Captain in the Army Medical Corps in World War I and practiced in Searsport and Dover, New Hampshire, locating in Kittery in 1919.

An honorary member of the York County Medical Society and the Maine Medical Association, he received a 50-year pin in 1965, a 55-year pin in 1970 and a 60-year pin in 1975. He was also secretary of the York County Medical Society for over forty years, served on the staff of the Massachusetts General Eye and Ear Hospital in Boston, and was a medical examiner for many years, as well as a public health officer.

Surviving are three daughters; Mrs. Connie Carmody of Portsmouth, Mrs. Barbara Hope of Kittery and Miss Priscilla Kinghorn of South Berwick; and three grandchildren.

## JEAN A. CURRAN, M.D.

1893-1977

Dr. Jean A. Curran, 84, of Cambridge, Massachusetts, died on January 16th.

Born in Ironwood, Michigan on January 12, 1893, Dr. Curran received an AB degree in biology from Carleton College in Minnesota. By the time he attended Harvard Medical School, he had taught high school science and worked as a hired hand on the farm of Dr. Charles Mayo, founder of Minnesota's famed Mayo Clinic.

A scholarship student, he worked as a busboy in the restaurant of the medical school and as a laboratory technician at Boston City Hospital. "A real part of Harvard's greatness," he once said, "is that a poor boy with ability is helped to get an education there."

He received his medical degree in 1921, and worked as an intern at the Brooklyn Hospital in New York. Shortly afterward,

he and his bride, the former Frances Rose of Pittsfield, a nurse he had met in Brooklyn, left for China, where they ran a small medical mission for five years.

In the early 1930's, Dr. Curran practiced medicine in New York City, and in 1934 he undertook what became a three-year study of internships and residencies available at New York hospitals. The study eventually became a book.

For the next twenty years, he worked as a medical educator, first as dean and then as president of the Long Island College of Medicine. He retired in 1956.

In December 1956, Dr. Curran was appointed a full-time consultant to the trustees of the Bingham Associates Fund, based at the Tufts-New England Medical Center in Boston.

Among his other projects as a consultant, Dr. Curran participated in studies of 50 hospitals in Maine affiliated with the Bingham fund.

Dr. Curran was a trustee of the New England Medical Center Hospital, a member of the advisory boards of the Newton Junior College School of Nursing and the University of Massachusetts School of Nursing.

He also served during World War II as a consultant to the Army's surgeon general and later as an advisor to the World Health Organization, for which he conducted a survey of medical schools in Egypt, Lebanon, Iran and Pakistan.

Dr. Curran is co-author of a report titled, "Unmet Needs in the Medical Care of Rural People, State of Maine, 1956," and of a book, "Founders of the Harvard School of Public Health, With Biographical Notes, 1909-1946."

Surviving are three sons, Jean, Jr., who lives in France; Dr. William of Albuquerque, New Mexico; and Robert, who serves with the foreign service in Afghanistan. He also leaves seven grandchildren.

## News, Notes and Announcements

**56th Annual Meeting  
New England Hospital Assembly Incorporated  
Boston, Massachusetts  
March 27-30, 1977**

**1977 Continuing Medical Education  
Summer Seminars  
Colby College, Waterville, Maine**

June 11-August 19 — The 32nd Annual Lancaster Course in Ophthalmology

June 25-26 — Third Seminar in Audiology

July 10-13 — 4th Annual Topics in Clinical Hematology

July 14-17 — 3rd Annual Topics in Clinical Oncology  
July 17-20 — 1st Annual Seminar in Pediatrics  
July 19-22 — 7th Annual Seminar in Surgical Techniques  
July 24-28 — 8th Annual Seminar in Neurosurgical Techniques  
July 27-30 — 1st Annual Seminar in Epilepsy  
July 31-August 3 — 18th Annual Seminar in Otolaryngology  
August 3-6 — 1st Annual Seminar in Dermatology  
August 7-11 — 3rd Annual Seminar in Ophthalmology  
August 14-18 — 1st Annual Seminar in Occupational Medicine  
August 14-19 — 9th Annual Seminar in Nuclear Medicine  
August 21-24 — 4th Seminar in Forensic Medicine  
August 21-25 — 4th Seminar in Pulmonary Disease

*Continued on Page 116*

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# THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

**Drug substitution** In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

**MAC** Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent,

generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

**The drug lag** The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than \$1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.



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For further information write to: Albert J. Finestone, M.D., Assistant Dean, Continuing Medical Education, Temple University School of Medicine, 3400 North Broad Street, Philadelphia, Pennsylvania 19140.

**Revised Laboratory Analysis Procedures on  
Blood Lead Analysis Procedures**

In accordance with The Center for Disease Control recommendations, the Public Health Laboratory will be utilizing the erythrocyte protoporphyrin (EP) test as a primary screening tool starting January 1, 1977. EP's will be done on all first tests sent to the laboratory. Positive EP's ( $60 \mu\text{g}/100 \text{ ml}$ ) will be confirmed with a simultaneous blood lead (Pb) analysis. All periodic blood tests (additional tests on previously identified victims) will be analyzed for both Pb and EP regardless of original results.

For further information regarding these procedures, please refer to The Center for Disease Control publication entitled "Increased Lead Absorption and Lead Poisoning in Young Children," March 1975. The publication is available from Medical Care Development, Inc., 295 Water Street, Augusta, Maine 04330.

**Annual Meeting of the Maine Chapter of the  
American Academy of Family Physicians**

The annual meeting of the Maine Chapter of the American Academy of Family Physicians was called by the President, Dr. John J. Pearson, of Old Town, at the Red Coach Convention

Center at Portland, Saturday, December 4, 1976. Prior to the meeting, a full day of seminars featuring problems of genitourinary origin was presented by the G.U. service of the Maine Medical Center and assisted by Dr. Martin Vickers, Jr. of Augusta.

Following the annual meeting, the members and guests were entertained by Marshall Dodd of "Bert and I" fame, a well-known after-dinner speaker and entertainer.

The following slate of officers was elected and duly installed by the National Vice-President, Dr. F. Woodward Lewis of Groton, Massachusetts who, with Mrs. Lewis, also a family physician and member, were honored guests.

President: Douglas R. Hill, M.D., 855 Sawyer St., South Portland

President-elect: John P. Dow, M.D., Grove Hill, Pittsfield

Vice-President: Edward P. Williams, M.D., 3 Mechanic St., Houlton

Directors:

Alex W. Jerome, M.D., 12 E. Chestnut St., Augusta

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Harold N. Burnham, M.D., 130 Main St., Gorham

Geraldine Lynn, M.D., 188 Russell St., Lewiston

Karl V. Larson, M.D., East Machias

E. Richard Bean, M.D., 121 Main St., Norway

Subsequent to this meeting and the holidays that followed, the entire membership, as well as the whole medical profession of the State, was saddened by the sudden death of our executive secretary-treasurer, Mrs. Ann Bostwick, wife of Dr. George Bostwick of Newcastle. It was through her efforts and painstaking perseverance, as well as her pleasant personality and ability, that the Maine Chapter has been so successful with the ever-increasing prominence of family practice. While it is humanly possible that someone may be found to continue her work, in the opinion of this writer there will never be anyone better.

JOHN J. PEARSON, M.D.  
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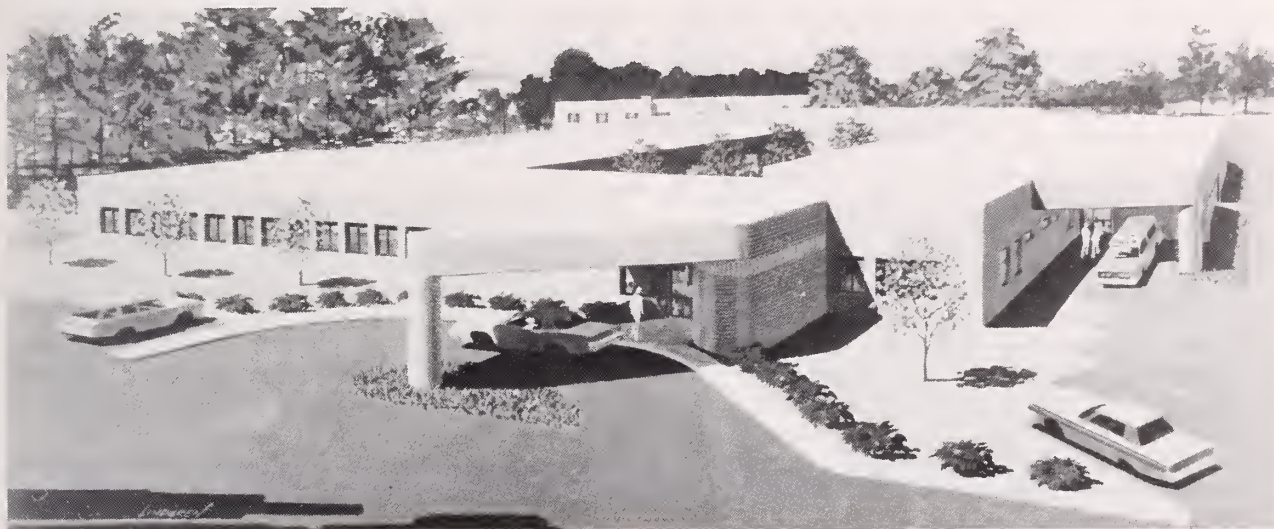


# The Journal of the Maine Medical Association

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## The Stephens Memorial Hospital Issue

"What are you doing in Norway, Maine?" That question, with various lifts of the eyebrow, has been asked of me many times in the past year by junketing physicians looking for a job, by friends in Academia and by relatives who somehow expected Something Else. It has been bothersome, in part, I think because I hadn't formulated a good answer. In the process of assembling the articles for this special issue of the Journal, it has dawned on me that the issue itself goes a long way toward answering that question.

For one thing, the medical climate here in conducive to the practice of good medicine. The hospital administrator, Harrison Hahn, and the board of trustees, chaired by Mrs. Hamilton O. Cornwall, have provided the medical staff with every facility, tool and electronic gadget it has required to deliver good care and to deal with most medical problems locally. As a consequence, the medical care here is excellent, and the community is aware of that. Community donations have accounted for half of the funding of the new hospital, soon to be completed independent of federal grants.

With this kind of support and cooperation from board and administration, attracting new physicians has not been difficult. Drs. Medd and Ware, whose papers in this issue reflect considerable expertise in

the fields of cardiology and oncology respectively, have established the specialty of internal medicine in this area. Dr. Sodhi, whose academic credentials are impressive by anyone's standards, directs the finest clinical laboratory of any I have dealt with in the past twelve years. The high standards of surgical care are reflected in Dr. Hamilton's article on tubal ligation. And the Old Guard maintains its energy. For a busy practitioner of twenty years to contribute to this issue says much about Dr. Harry Harper.

This kind of medical milieu, provided in large measure by the people mentioned above, has given me the feeling that, if you really want to be a Doctor, Norway, Maine, is where it's at. That answers the question.

To assemble an article like this, one needs patience, an ability to badger and a great deal of help. Two who have helped me immensely with editing and typing are Candy Anderson and Sandy Clark. "It just doesn't sound right," and "Maybe you meant to say . . ." have contributed a great amount to this Stephens Memorial Hospital Issue. Thank you, Candy and Sandy.

MICHAEL A. LACOMBE, M.D.  
17 Winter Street  
Norway, Maine 04268

# Preservation of the Ischemic Myocardium

## A Review of New Concepts in the Treatment of Acute Myocardial Infarction and Unstable Angina

WILLIAM L. MEDD, M.D.

### INTRODUCTION

The management of acute myocardial infarction took a dramatic step in the 1960's with the advent of antiarrhythmic therapy and Coronary Care Units. With this change in therapy came the survival of many patients who would have died from arrhythmias despite a reasonably healthy myocardium. Out-patient prevention of sudden electrical death continues to be a major problem despite mobile coronary care units which, when utilized, do decrease arrhythmia death. The major problem remains the lack of reliable, nontoxic, oral antiarrhythmic agents for the high-risk patient.

Another serious problem involves prolonged delay between onset of symptoms and arrival at a medical facility. This problem is multifactorial centering around several issues. Patients frequently ignore symptoms that are prodromal to an acute coronary event. Frequently patients prolong their call for help because they are afraid; don't want to bother the doctor; think the pain will go away. These difficulties can be dealt with by better patient education, but it will always be difficult to deal with the human element in disease.

Assuming the patient reaches medical help for his acute coronary event, the next problem becomes the prevention of myocardial necrosis or limiting its extent. The purpose of this review is to summarize basic and clinical research in this area and to put this information into perspective with regard to clinical management of coronary events. Because the majority of acute coronary events present to the local hospital, it is important for the practicing physician to understand and utilize these newer concepts.

### BASIC RESEARCH IN THE CELLULAR EVENTS OF ACUTE MYOCARDIAL INFARCTION

It seems well-established that once a coronary vessel becomes narrowed enough, the myocardium dependent on that vessel for nutrition develops ischemia. The mechanism of coronary narrowing continues to elude us, but it is known that there is a critical level of coronary flow needed to sustain myocardial cell viability. Once unremitting ischemia begins, cell death and necrosis occurs. At that point a vicious cycle can begin. Braunwald refers to a cycle where ischemia leads to necrosis which then leads to left ventricular dysfunction. As a result, systolic pressure begins to fall, further jeopardizing myocardium that is still only ischemic and then causing microvascular obstruction and

further cell necrosis.<sup>1</sup> Finally, pump failure occurs and, ultimately, death. This sequence of events takes time. If the ischemic zone outside the area of necrosis can be salvaged, the size of the myocardial infarction is reduced. The end result is better left ventricular function following a myocardial infarction.

Many events play a role in cell death. Ischemic effects on the myocardium seem to be related to lowering of intracellular pH due to lactate build-up. This decreases the rate of energy production. Alteration in the calcium cycle due to acidosis in the myocardium may be the ultimate cause of decreased energy production.<sup>2</sup> According to Jennings, "The primary event leading to irreversibility may be the sarcolemmal defect which allows excess calcium to enter the injured cell."<sup>3</sup> Cell swelling occurs as the above-mentioned events take place. Because of membrane and cell pump dysfunction, sodium is not extruded from the cell, and intracellular edema occurs.

### ANIMAL EXPERIMENTS IN ALTERING MYOCARDIAL ENERGY SUPPLY AND DEMAND

The above events occur because of a lack of energy supply to the myocardial cells. It is important to understand the basic concept of the balance between energy supply and demand, which, when altered, is the basic defect that leads to ischemia and necrosis. Myocardial oxygen consumption (work or demand for energy) depends on the pressure developed by the left ventricle. The peak velocity of the contraction of the myocardium (inotropic state) is another determinant of myocardial oxygen consumption. Finally, heart rate reflects myocardial oxygen consumption due to increased frequency of contraction or number of times tension is generated.

Using the assumption that reduction in the myocardial oxygen consumption would decrease in coronary occlusion, Maroko and Braunwald conducted experiments on anesthetized dogs.<sup>5</sup> They used ST segment mapping with direct epicardial lead placement to reflect severity of ischemic injury. This technique will be described later on in this review. They showed that interventions increasing myocardial oxygen consumption in non-failing hearts — isoproterenol, digitalis, glucagon, bretylium and atrial pacing — all increase the severity and extent of myocardial injury. An attempt to reduce myocardial oxygen consumption was carried out with Beta blockers, and myocardial injury was reduced. Digitalis in the failing heart decreased

myocardial injury because it decreased oxygen consumption by improving myocardial performance. They noted hypotension (a decrease in oxygen supply) increased injury, and hypertension (improved oxygen supply) decreased myocardial injury.

Approaching the problem metabolically, Maroko and Braunwald review the data on enhancing anaerobic glycolysis.<sup>6</sup> When the myocardial cell is deprived of oxygen, it employs anaerobic metabolism. If glucose-insulin-potassium solutions are infused, glycogen is increased in the cell, allowing the cell to withstand anoxia. Consequently, epicardial mapping revealed a reduction in injury with glucose-insulin-potassium infusion.

In addition, it is possible to improve delivery of oxygen to myocardial cells thereby increasing anaerobic metabolism. One way is by improving the intrinsic collateral circulation. However, this is difficult to achieve due to the high resistance of the collateral circulation.<sup>7</sup> Another is by increasing the inspiratory oxygen concentration. Improved oxygenation decreases anaerobic metabolism and improves the acid-base balance of the myocardial cell.

Other means of improving the balance between oxygen supply and demand were reviewed by Maroko and Braunwald in the same article.<sup>8</sup> Hyaluronidase, which increases diffusion through the extracellular space, was evaluated. With improved delivery of substrate to the jeopardized myocardial cell, it appears that injury is diminished. This enzyme may work by depolymerizing hyaluronic acid and increasing capillary permeability. As mentioned earlier, cell swelling is a major problem in myocardial necrosis. Studies done by Powell, et al, demonstrated that hyperosmotic Mannitol administered to dogs with occluded coronaries resulted in improved function of the canine heart with a decrease in extent of ischemic injury assessed by ST segment mapping.<sup>9</sup> These studies confirm a reduction in extent of eventual myocardial necrosis with a decrease in cell swelling. Hydrocortisone was tested. It reduces infarct size in dogs, possibly due to protection of lysosomes and stabilization of phagocytic vacuoles. However, in human studies there is much debate over the role of cortisone in acute myocardial infarction. Roberts, et al, found that methylprednisolone increased infarct size and the incidence of malignant dysrhythmia.<sup>10</sup>

It is necessary to clarify the terms afterload and preload before proceeding. The former refers to the pressure the heart has to pump against to promote blood flow. The latter term refers to the volume the heart must handle with each cardiac cycle. Experiments have been done with vasodilator drugs which reduce afterload. DaLuz, et al, measured left ventricular function and lactate production following left anterior descending coronary occlusion in twenty-one dogs.<sup>11</sup> Their results indicated that nitroprusside, a potent vasodilator, improved cardiac performance and mechanical performance of a re-

gionally ischemic myocardium. In addition, lactate production seemed to decrease.

#### TECHNIQUES USED TO MEASURE MYOCARDIAL ISCHEMIA AND NECROSIS

A crucial aspect of all the basic research is the technique used to determine whether or not myocardial injury is being influenced by the various interventions discussed above. The use of CPK enzymes and precordial mapping seem to be the most reliable at present.<sup>12</sup> Many researchers have established that CPK changes correlate closely with infarct size, functional cardiac impairment and severity of clinical dysfunction. However, the length of time needed to obtain the results of CPK determinations limit the use of CPK's to assess rapidly the results of intervention in the acute setting.<sup>13</sup>

The use of ST segment analysis is a promising way of monitoring rapid changes in myocardial injury.<sup>14</sup> It is somewhat tedious in that a map is made of the precordium using up to 48 leads placed exactly each time. The area under each ST segment is then summed to obtain a total figure. This technique demonstrates rapid changes and will detect improvement or deterioration in ischemia with regard to therapeutic intervention. It is most reliable for anterior and lateral myocardial infarctions. A word of caution needs to be interjected since some researchers feel precordial leads aren't as reliable as epicardial leads.<sup>15</sup> In addition, newer equipment needs to be developed to get reliable serial ST determinations and rapid results.

Other potentially helpful techniques include Echocardiography and isotopic scanning. Echocardiography looks for changing patterns in myocardial wall function. It is not refined enough at present nor able to isolate small enough areas of myocardium to be helpful. <sup>99m</sup>Tc-tetracycline and <sup>99m</sup>Tc-pyrophosphate when injected intracoronary or intravenously will be taken up in areas of myocardial necrosis. Radioactive potassium will demonstrate areas of decreased perfusion when injected into the coronary arteries. The obvious drawback of this latter test is the need for coronary catheterization. Hopefully in the future, an intravenous injection of radioactive potassium or some other element will accurately and quickly establish areas of decreased perfusion. The technique to establish areas of necrosis is becoming more usable with portable Gamma cameras and the use of intravenous material. However, in an attempt to reduce ischemia, we need to evaluate perfusion of the myocardium. At present, the most reliable technique is by intracoronary injection of radioactive potassium.

Finally, a reliable tool is now available to assess left ventricular function and the affect medical intervention is having on hemodynamics. The Swan-Ganz catheter measures the wedge pressure which, in most instances, correlates closely with left ventricular end diastolic pressure. End diastolic pressure reflects changes in left ventricular func-

tion. In addition, the cardiac output and cardiac index can be determined in the Intensive Care Unit.

#### CLINICAL APPLICATION OF BASIC RESEARCH IN ACUTE MYOCARDIAL INFARCTION

With animal experiments demonstrating the ability to alter the process of myocardial necrosis and with techniques to measure results of intervention, it is now logical to review data obtained from human clinical trials. At present, the most published method of altering infarct size is vasodilator therapy. One of the major findings that lead to the use of vasodilatation in the acute ischemic situation was the finding that nitroprusside improved left ventricular function in chronic congestive heart failure. Palmer and Lasseter have reviewed the action of nitroprusside.<sup>16</sup> It is a peripheral arterial and venous vasodilator and possibly a coronary vasodilator. Several studies have shown that vasodilatation reduces impedance to left ventricular ejection (afterload), thereby lowering the left ventricular end diastolic pressure, increasing cardiac output and increasing stroke volume. The systemic pressure drops only slightly in these studies.<sup>17,18</sup> Another study demonstrated the long-term benefit in chronic congestive heart failure which chewable isosorbide dinitrate.<sup>19</sup>

The above results were obtained in patients with chronic congestive heart failure stemming from ischemic heart disease. Similar results have been demonstrated in chronic congestive heart failure due to aortic regurgitation<sup>20</sup> and mitral regurgitation.<sup>21</sup> The use of vasodilator therapy has been explored in congestive heart failure secondary to acute myocardial infarction. Gold, et al, showed sublingual nitroglycerine improved cardiac output and dropped left ventricular end diastolic pressure in the face of an acute myocardial infarction.<sup>22</sup> In turn, Swan's group has been using vasodilator therapy in cardiogenic shock complicating acute myocardial infarction.<sup>23</sup> With careful monitoring of wedge pressure and cardiac output, they used intravenous nitroprusside, nitroglycerine or phenolamine. Patients with elevated left ventricular end diastolic pressure and lowered stroke work indices showed improvement. In a series of forty patients with severe pump failure and/or cardiogenic shock, they were able to drop the mortality by 42%.

Vasodilator therapy has been used to decrease infarction size in humans. One of the first studies used CPK's to determine infarct size and trimethaphan (a ganglionic blocker) to lower systolic pressure in hypertensive myocardial infarctions.<sup>24</sup> These workers found a 24% reduction in predicted infarct size. This data suggests that a hypertensive response to an acute myocardial infarction is deleterious and that by lowering blood pressure infarct size can be reduced.

In addition to this, Flaherty, et al, administered intravenous nitroglycerine (not available for clinical use) to patients with acute myocardial infarctions and noted a decrease in left ventricular filling pres-

sure with only a 7 millimeter decrease in mean arterial pressure and a decrease in the sum of ST segments using precordial mapping. This data suggests that intravenous nitroglycerine improved left ventricular function and decreased myocardial ischemia.<sup>25</sup>

The beneficial role of afterload reduction with nitroprusside is not clear. Magnusson, et al, used nitroprusside to lower patient's systolic pressure from an average of 144 to 128 and noted a rise in CPK values compared to control subjects.<sup>26</sup> Maroko noted nitroglycerine and nitroprusside improved hemodynamics, but nitroprusside increased ST elevation when using the ST summing technique to measure ischemia.<sup>27</sup>

Nitroglycerine would appear to be a better vasodilator because of its direct effect on myocardial circulation. Nitroglycerine favorably alters the distribution of blood in the myocardium by promoting flow selectively to the subendocardial zone.<sup>28</sup> This may be due to selective vasodilatation of the penetrating arteries delivering blood from epicardium to endocardium. In addition, nitroglycerine seems to improve contraction of asynergistic areas in the myocardium. Nitroprusside appears to affect the larger coronary vessels only.

However, there is data that has been presented by Williams, et al, suggesting that nitroglycerine might be deleterious.<sup>29</sup> In their experience, they found sublingual nitroglycerine useful in relieving pulmonary congestion and decreasing myocardial oxygen consumption, but they found a deleterious fall in cardiac output and systemic blood flow. They feel that nitroglycerine causes primarily venodilatation and, therefore, a reduction in preload or blood volume entering the heart. This, compounded by hypotension, seems to worsen overall pump function.

Studies by Borer, et al, have helped resolve the mixed results that have been reported with the use of nitroglycerine in reducing myocardial infarction size.<sup>30</sup> They studied twelve patients (five had left ventricular failure) by using ST mapping to assess ischemia. The patients without failure did not benefit from nitroglycerine alone, but the addition of phenylephrine did cause a decrease in the sum of ST segments. In the patients with heart failure, nitroglycerine alone reduced ischemia. This reduction of ischemia was partially reversed if phenylephrine was added to the patients with failure, suggesting that improvement in failure by afterload and/or preload reduction was more important than the primary effect of nitroglycerine on the myocardium. This latter effect seems helpful if the patient is not in failure and the peripheral side effects of the nitroglycerine are counteracted with phenylephrine or methoxamine which counteracts the hypotension and tachycardia that can occur with nitroglycerine.

Several other approaches have been investigated in attempts to preserve the ischemic myocardium. Mueller, et al, administered I.V. Propranolol to twenty patients with uncomplicated acute myocar-

dial infarctions.<sup>31</sup> They found a decrease in cardiac index, a slight increase in wedge pressure (2 millimeters of mercury) but a marked improvement in myocardial metabolism. Also, they found a decrease in coronary blood flow. They concluded that the improvement in myocardial metabolism suggested that the decrease in myocardial oxygen demand was more important than decrease in coronary blood flow.

Hyaluronidase has been evaluated in humans with acute myocardial infarction. Maroko, et al, compared thirteen patients with acute myocardial infarctions who received hyaluronidase to eleven patients who did not by means of ST mapping.<sup>32</sup> In the treated group there was a 38.3% greater drop in the sum of the ST segments at twenty-four hours compared to the control group. Again, this suggests reduction in ischemic injury. Brachfeld's review on glucose-insulin-potassium sums up the current confusion as to whether this is beneficial in humans.<sup>33</sup> There have been numerous studies with mixed results. At present it is my opinion that it does not appear to be harmful and may be helpful in reducing ischemic change.

#### CLINICAL APPLICATION OF NEWER METHODS IN UNSTABLE ANGINA PECTORIS

To begin, it is necessary to review the traditional approach to unstable angina. This should include looking for obvious concurrent medical problems that are causing undue myocardial oxygen consumption. One must look for untreated hypertension, hyperthyroidism, anemia, hypoxia, increased anxiety and subclinical hypovolemia as seen in slow gastrointestinal oozing of blood. When obvious causes of unstable angina have been excluded, the primary problem of unstable angina can be approached. It basically represents an oxygen supply and demand problem leading to intermittent ischemia without necrosis. At this point it is crucial to treat coronary disease because symptoms occur before cell necrosis. Therefore, controlling oxygen demand and improving oxygen supply is the ultimate step in preservation of the ischemic myocardium. To begin, one uses long-acting nitrates if they don't cause hypotension, both for the effect on redistribution of coronary blood flow toward the endocardium and for reduction in preload and possibly afterload. At present, nitrate paste seems to offer the best means of obtaining prolonged blood levels of nitrate, although the delivery is erratic. Chewable and sublingual nitrates are acceptable alternatives, but their action is brief.

Propranolol (a beta blocker) is used to reduce oxygen consumption by the myocardium. It is used with caution, watching carefully for congestive heart failure or bronchospasm. If these problems do not occur, then doses up to 400 mg. a day may be used rather safely. If the patient has cardiomegaly, the concomitant administration of digitalis is indicated. The latter drug might decrease angina alone if the patient is in failure by improving myocardial

performance, thereby decreasing oxygen consumption. If the above techniques do not control recurrent unstable angina, this author has begun to try vasodilator therapy in low doses in patients who develop acute hypertension just before an angina attack. James, et al, have recently discussed a cardiogenic hypertensive chemoreflex which seems to be a chemoreceptor near the origin of the left main coronary.<sup>34</sup> This is responsive to ischemia and initiates a hypertensive response. If this is significant, it would increase the work of the myocardium at a time when supply was diminished. If a reasonable medical approach does not work, then it is time to consider surgical intervention. I do not advocate immediate surgical intervention before medical therapy. This is supported by a recent review by Scheidt, et al.<sup>35</sup> When surgical intervention appears inevitable, the intra-aortic balloon is frequently used to reduce the workload on the myocardium and to improve perfusion of the coronary circulation during diastole. Then the patient undergoes coronary angiography and, if operable, will have the appropriate vein grafts put in place. As of now, the results of surgery appear to be excellent.<sup>36</sup> For the inoperable, incapacitated patient with angina, however, there are other approaches. First is the rendering of the patient hypothyroid to lower oxygen consumption in the heart by decreasing overall metabolism. The second is the use of potent analgesics — a mode of therapy not often considered.

#### CONCLUSION

There are many facets of the care of the patient with coronary atherosclerotic heart disease. Above I discussed the current approach to unstable angina which is an exciting and challenging entity because, by preventing a myocardial infarction, we have salvaged healthy myocardium. Before a patient develops clinical coronary disease, it would be nice to have intercepted the inevitable by diet and drug management. However, this has not been terribly fruitful to date. In addition, we have the terribly complex problem of personalities, which seem to play a role in terms of the risk factor of developing coronary disease. Trying to get a type A personality to switch to a more blissful type B personality is no easy task. In addition, the cigarette appears to be here to stay. Consequently, we will continue to have to deal with acute myocardial necrosis for years to come.

From this review, it appears we are beginning to move toward limiting the area of damage during an acute myocardial infarction. According to Pitt, left ventricular function is a major factor in long-term survival post acute myocardial infarction.<sup>37</sup> One set of figures states that patients with severe left ventricular dysfunction show a five-year survival of 38% compared to 77% in those without left ventricular failure. Because infarct size is so important, it is imperative for the physician to see patients when they present with acute necrosis to be aware of the

newer concepts of therapy. At present, much remains experimental, but some of the experimental results now seem applicable.

It is very important to monitor acute myocardial infarctions carefully in a Coronary Care Unit. If other than routine treatment is undertaken, a Swan-Ganz catheter is essential. If attempts to actively preserve ischemic myocardium are undertaken, then one must be able to monitor drug effects. This includes close blood pressure and wedge pressure monitoring to follow left ventricular function. Certainly, the ability to determine cardiac output would be helpful but not essential if one follows the wedge pressure, urine output and blood pressure. As soon as an accurate means to assess perfusion of myocardium becomes available, this will be an essential element in trying to preserve marginal myocardial cells. The routine patient with myocardial infarction, normal blood pressure, no congestive heart failure and a brief duration of pain should be treated conservatively. If experimental data confirms that intervention may decrease the size of their myocardial infarction, then we may need to reconsider intervention in the future. The patient with significant hypertension should be treated with nitroprusside or phentolamine. The former is preferable because of its brief duration of action. If this intervention causes the wedge pressure to rise or the pain to increase, then the pressure should be allowed to rise again because coronary perfusion is probably dependent on the patient's elevated pressure. However, I have yet to experience this.

The patient who has an acute myocardial infarction with congestive heart failure may respond to preload reduction via diuretics and improved left ventricular function with digitalis. However, if he doesn't improve, then he too is a candidate for vasodilator therapy. The same patient who is hypotensive is a more serious problem. He should have wedge pressure monitoring and a trial of vasoconstrictive therapy with dopamine or levarterenol. If this is ineffective, I would use vasodilator therapy cautiously, being careful not to drop the systolic pressure below 70 or 80 millimeters of mercury. The urine output must be measured carefully.

One should not forget that a few patients who appear to be in cardiogenic shock respond well to volume, bringing the end diastolic pressure to the optimum level of 15. This end diastolic pressure seems to be the optimal filling pressure for maximal left ventricular function in the face of an acute myocardial infarction.

The patient with prolonged pain is a difficult patient to manage. Using a Swan-Ganz catheter and finding the wedge pressure less than 15, I would consider low-dose Propranolol with close observation of the wedge pressure. In addition, sublingual nitroglycerine and/or nitrate paste could be used with careful attention to hypotension and tachycardia. If this occurs, methoxamine or phenylephrine should be used. If the wedge pressure is elevated,

nitroglycerine alone or intravenous nitroprusside should be tried. Hopefully, intravenous nitroglycerine will soon be available for clinical use. The data for reducing myocardial infarction size seems good, but interventions in the patients with prolonged pain is still experimental. However, surgical intervention in this type of patient with an acute myocardial infarction is not without risk. I feel, with close monitoring and rapid-acting drugs, one can intervene medically with little risk of worsening the situation. In fact, at present it looks like we may be at a frontier in terms of salvaging viable myocardium.

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*Continued on Page 131*

# Neurological Complications of Malignant Lymphomas

DONALD E. WARE, M.D., W. A. ROBINSON, M.D. and JOHN E. KURNICK, M.D.

## INTRODUCTION

Malignant lymphomas often cause neurological problems. These problems can be the first manifestation of the malignant process or can arise during the course of the disease. The former is much less common than the latter. Malignant lymphomas can lead to cord compression, central nervous system lesions, and cranial and peripheral nerve damage. Malignant lymphomas also predispose to infections of the neurological system.

Noninfectious neurological complications of malignant lymphomas at the University of Colorado Medical Center were reviewed. Thirty-seven patients with malignant lymphomas had neurological complications during the period from 1960 to 1972. In each case, the neurological problem was suspected to be secondary to the lymphomatous process but this was not always proven.

## RESULTS

Eighteen female and nineteen males were seen with neurological problems. Table 1 shows the breakdown as to the type and number of malignant lymphomas seen in these patients. The figures of the total number of patients seen at the University of Colorado Medical Center with each type of lymphoma were gathered from the Tumor Registry of the Medical Center.

Table 2 shows the clinical stage of the disease at the time of the neurological complication. The patients in whom the stage was unknown are not included in the table. Also included in this table is the type of therapy the patients were receiving at the time they developed the neurological problem.

Several different types of nervous system involvement were seen. All were considered clinically to be secondary to the patients' lymphoma. In only some of the cases was histologic proof obtained either by biopsy at the time the complication arose or at autopsy. Table 3 shows the sites of involvement and the number of times that each site was involved. Some patients had more than one site involved and are entered under two different categories. Twenty patients with malignant lymphoma involving their epidural space were seen. As other authors have pointed out, the signs and symptoms of these patients were similar to the signs and symptoms of patients with any space occupying lesion of the epidural space. Table 4 shows the presenting chief complaint of the patients with epidural involvement. Almost 60% of the patients gave a chief complaint of back pain.

The response to therapy of patients with lymphoma of the epidural space was reviewed. Table 5 shows the results. The patients have been divided into 5 categories depending on their signs and symp-

TABLE 1

<i>Types of Lymphomas Seen</i>	<i>Number of Patients With Neurologic Complications</i>	<i>Total Number of Patients Seen</i>
Hodgkin's disease	17	80
Lymphosarcoma	9	93
Reticulum Cell Sarcoma	10	50
Giant Follicular Lymphoma*	1	2

\* At the time of the neurologic complication the histologic pattern was diffuse lymphosarcoma-lymphocyte poor.

TABLE 2

CLINICAL STAGE OF LYMPHOMA AND THERAPY AT TIME OF NEUROLOGIC COMPLICATION			
		A	B
Stage I	2	2	0
Stage II	1	0	1
Stage III	3	0	3
Stage IV	27	0	27
Chemotherapy	28		
Radiotherapy	4		
None	5		

TABLE 3

SITES OF INVOLVEMENT OF THE NERVOUS SYSTEM		
Epidural Space		
Number of patients	20	
Cervical segment	2	
Thoracic segment	13	
Lumbar segment	9	
Sacral segment	1	
Central Nervous System		
Number of patients	12	
Brain	11	
Spinal Cord	1	(Intramedullary C-5-6)
Peripheral Nerves		
Number of patients	4	
Brachial plexus	2	
Recurrent laryngeal	2	
Cranial Nerves		
Number of patients	2	
III, VI, VII		
Primary Central Nervous System Tumor	1	
(glioblastoma multiforme)		

TABLE 4

PRESENTING CHIEF COMPLAINT OF PATIENTS WITH EPIDURAL LYMPHOMA	
Back Pain	12
Bladder or Bowel Dysfunction	2
Motor Weakness	2
Paresthesias	3
Sensory Loss	1

phoma of the epidural space was reviewed. Table 5 shows the results. The patients have been divided into 5 categories depending on their signs and symp-

TABLE 5

SIGNS AND SYMPTOMS OF PATIENTS WITH EPIDURAL LYMPHOMAS AS THEY RELATE TO RESPONSE TO THERAPY				
Signs and Symptoms	# Patients	Therapy	Results	
I. Back pain with positive myelogram but without neurological defect	1	Radiation	No residual	
II. Back pain with positive myelogram and paresthesias	4	Radiation	No residual	
III. A. Back pain with motor weakness without bladder or bowel dysfunction	6	5 radiation 1 radiation & laminectomy	1 gradual improvement 4 residual weakness 1 lost to follow-up	
III. B. Back pain with motor weakness with bladder or bowel dysfunction	3	Radiation	3 residual weakness 2 residual bladder or bowel dysfunction 1 normal bladder & bowel function	
IV. Motor paralysis	4	Radiation	2 no improvement* 1 profound motor weakness** 1 died during therapy	
V. Bladder or bowel dysfunction only	2	Radiation	1 no residual 1 died during therapy	

\*onset of neurologic symptoms sudden

\*\*onset of neurologic symptoms slow with back pain for 5 months

TABLE 6

SUMMARY OF 13 PATIENTS WITH CENTRAL NERVOUS SYSTEM ABNORMALITIES					
Brain Symptoms	Type of Lymphoma	Diagnostic Studies	Tissue Diagnosis	Therapy	Result
Headache	HD	Increased CSF protein & pressure	yes	Nitrogen mustard radiation	improved
Headache	LSA with blood involvement	Increased CSF protein	yes	BCNU Intrathecal methotrexate	died
Headache	LSA	Normal CSF protein 2 rt. parietal masses by angiogram	biopsy of brain normal	radiation	improved
Headache and paralysis of left eye	RCS		yes	radiation	improved both headache and paralysis
Headache	RCS	Parietal mass by scan	no	radiation	improved
Dementia	HD		yes	none	died
Decreased vision	HD	visual defect	no	radiation	no improvement
Double vision	RCS	left parietal mass	no	radiation	died
Decreased responsiveness					
Lethargy progressing to coma	RCS	abnormal EEG abnormal brain scan	no	radiation	taken from hospital by family
Seizures	HD		no	none	died
Disorientation	HD	EEG-slowness in post hemisphere angiogram-hydrocephalus pneumoencephalogram-hydroenceph. cortical atrophy	no	radiation  velban	no improvement improvement
Confusion, nausea, vomiting	LSA with blood involve.		yes, glioblastoma multiforme	none	died
Cord	Type of Lymphoma	Diagnostic Studies	Tissue Diagnosis	Therapy	Result
Loss of function of hand	RCS	Myelogram-intramedullary mass	yes	radiation	initial slight improvement

HD = Hodgkin's disease

LSA = Lymphosarcoma

RCS = Reticulum cell sarcoma

toms at the time of therapy. The table also shows the modality of therapy used.

Table 6 shows the presenting signs and symptoms of patients with malignant lymphoma involving the central nervous system. Also included in this table is the type of treatment given and the response to that treatment.

The cranial nerve lesions and peripheral nerve lesions showed signs and symptoms expected with the specific nerve involved were the brachial plexus and recurrent laryngeal nerves. Of the four patients with peripheral nerve involvement and the two patients with cranial nerve involvement, only two patients had their nerve deficit resolved with local

irradiation. The nerve deficit remained unchanged in one patient following local irradiation. Two patients died during their therapy without change, and one patient was not treated specifically for the nerve deficit.

### DISCUSSION

Neurological complications are a relatively common problem seen in patients with malignant lymphomas. As can be seen from Table 1, this complication can occur in any one of the group of malignant lymphomas. The total number of patients recorded at the University of Colorado Medical Center with malignant lymphomas from 1960 to 1972 is probably inaccurately low. There was a period of time when not all malignant lymphomas were recorded in the Tumor Registry. However, using these figures, the overall incidence of neurological complications arising in patients with malignant lymphomas in this series is 16 percent. Williams, et al state that "13 percent of 5,778 lymphoma and leukemia patients had some type of nervous system involvement."<sup>1</sup> Currie and Henson studied 774 patients with reticulosos. Twenty-six percent of their patients developed neurological syndromes.<sup>2</sup> Both of these studies included infectious complications. Verity showed an incidence of 7.6% of his patients with Hodgkin's disease manifested neurological complications.<sup>3</sup> The exact percentage of those patients with malignant lymphomas that will develop neurologic complications is not important. What is important to realize is that it is not a rare occurrence.

Table 2 shows that the majority of the neurological complications occurred in patients with widespread disease. Only two of the 33 patients in whom the clinical stage of the disease was known, did not have systemic symptoms of fever, weight loss, or night sweats at the time of their neurological complication. Only three patients of the 33 had disease limited to one side of the diaphragm. In one of these three patients, the neurological complaint was the presenting symptom. The data show that the neurological complications occur most often in patients with far advanced disease with systemic symptoms.

Also of interest is that most of the patients were receiving some form of therapy at the time of the neurological complication. Only five out of 37 were not receiving therapy. This seems to show that ongoing therapy is no protection against developing neurological complications.

Epidural space involvement is the most common neurological site involved with lymphoma. The most common epidural area was the thoracic segment followed by the lumbar region.

The central nervous system was involved about one-half as often as the epidural space. This finding is in agreement with other series which found that cranial involvement is less common than epidural involvement.<sup>1,4,5</sup> The diagnosis of intracranial involvement is a difficult one and is often not sup-

ported by histological evidence. Only six of the twelve patients had a positive tissue diagnosis. Most of the central nervous system involvement is found in the dura or meninges. The lymphoma then extends along vessels and nerve roots.<sup>1,3</sup>

Four patients had peripheral nerve involvement. Currie and Henson found peripheral nerve involvement unusual in their series.<sup>2</sup> Williams, et al found it in 2.25% of their cases.<sup>1</sup> Williams et al found the brachial plexus most commonly involved, followed by the cervical sympathetics and the recurrent laryngeal.<sup>1</sup> These areas are obviously located near lymph node areas often involved in the malignant process.

Two patients had cranial nerve involvement. One had diffuse arachnoid and subarachnoid involvement at autopsy. The other had large nodes around the orbit. These cases seem to represent the two main mechanisms of cranial nerve involvement; either direct compression of the nerve by the lymphatic process near its exit from the skull or meningeal involvement.

One patient had a primary malignancy of the central nervous system. Involvement of the central nervous system was suspected before death, but the etiology of the involvement was not known until autopsy. This patient had been treated with "immunosuppressive therapy." Nothing can be said about the incidence of this occurrence with only one patient; however, lymphomas do predispose to the development of another malignancy.<sup>11</sup> Also, treatment with chemotherapy and radiation may play a role in the development of a second malignancy.<sup>12</sup>

Two other patients were initially diagnosed as having primary central nervous system tumors. Upon review of the pathological material in light of the diagnosis of existing lymphoma, it was felt that the lesions represent lymphomatous processes. This points out the difficulty in diagnosing malignant lymphoma of the central nervous system pathologically. This is particularly true of reticulum cell sarcoma.

If correction of the neurological problem is to be obtained, a correct diagnosis must be made early in the clinical course. The presenting complaints of patients with epidural masses are shown in Table 4. The symptoms are often non-specific. The most common symptom was back pain. This complaint in a patient with malignant lymphoma (especially if the disease is far advanced) should alert the clinician that the patient may have epidural involvement. In our experience this symptom was often followed for several visits until another more ominous sign became manifest. It is imperative that a patient with this symptom of back pain be further evaluated with an extensive neurologic examination, spinal x-rays, and possibly a myelogram. A myelogram, if done when the patient only has back pain, and before the disease has progressed to cord compression, most likely will show an epidural space occupying lesion.<sup>6</sup> At this point therapy could be instituted and cord

compression avoided. Love, et al point out that in patients with disease presenting initially with epidural involvement, only 33% have positive vertebral lesions on x-ray.<sup>7</sup> Williams, et al state that out of 97 patients with cord compression, the spine x-rays were normal in 56.<sup>1</sup> Thus, the spinal x-ray is not an adequate exam to rule out epidural lymphoma. Mullin, et al state that "myelography be performed even in the absence of a neurologic deficit in cases of malignant lymphoma with otherwise unexplained and significant back or radicular pain."<sup>6</sup> Table 5 points out the importance of this statement. It can be seen that the milder the symptoms of compression, the more successful is the therapy. Only one patient had myelography for back pain *before* another neurological sign or symptom developed. This points out the difficulty in diagnosing this problem. The goal, of course, is to make the diagnosis before neurological damage has been done. After the symptoms from compression have developed, therapy is much less successful. Signs of motor weakness and bladder or bowel dysfunction carry a particularly poor chance for successful therapy. Paresthesia without other neurological signs, on the other hand, seem to carry a good prognosis for recovery.

All of the patients in this series were treated with radiation. One was treated with radiation and laminectomy. Rubin, et al state that high daily dose irradiation is an excellent means of relieving spinal cord compression of epidural lymphoma.<sup>8,9</sup>

Table 6 is a summary of the 13 cases with central nervous system involvement. The symptoms are many and varied. Histological proof is difficult to obtain and treatment was often based on clinical impression alone. Thompson, et al state that brain scans may be helpful in making the diagnosis of central nervous system lymphoma.<sup>10</sup> Therapy was of benefit in eliminating symptoms in one-half of the cases. Radiation therapy relieved the symptoms of 7 out of 8 patients in the series by Thompson, et al.<sup>10</sup>

In summary, several points should be reiterated.

Neurological complications of malignant lymphomas are not uncommon. They usually occur in patients who have far advanced active disease. The epidural space is the most common site of involvement. The earlier the epidural involvement is diagnosed, the more successful will be the therapy. It appears that myelography should be carried out on patients with malignant lymphoma with significant back pain but without other neurological symptoms or signs. The malignant lymphoma also causes neurologic complications in the central nervous system, peripheral nerves, and cranial nerves.

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# Organization and Results of a Risk Factor Screening Clinic

HARRY L. HARPER, M.D.\* and DENNISE WHITLEY\*\*

Stephens Memorial Hospital in Norway, Maine, is a community funded institution, built solely by public donation in 1957. The hospital serves 21,000 people, which includes the population of Norway and South Paris and the many surrounding rural communities. Interaction between the community and hospital is therefore most important for continued community support of the hospital facility.

The hospital Public Relations Director was informed of a Risk Factor Screening Program sponsored by the Maine Heart Association which had been done on a limited basis in a few communities in the State. To promote community-hospital interaction and to advance health care in this area, Stephens Memorial Hospital chose to co-sponsor a Risk Factor Screening Program for coronary artery disease and hypertension as its project for National Hospital Week in May of 1974.

The organization and aims of the Risk Factor Screening Program for coronary artery disease and hypertension are outlined as follows:

## I. PROGRAM AIMS:

1. To educate individuals concerning risk factors associated with heart disease and hypertension, to urge them to modify their lifestyles, and if test results so indicate, to motivate them to seek medical advice.
2. By using the expertise of a State health agency and enlisting the support and cooperation of all health related organizations in the community, to effectively prove the value of a combined effort directed toward health education.
3. To motivate industries in the community toward the realization of their responsibilities for providing preventive health care and education for employees when available.

## II. PROGRAM PLAN:

The Risk Factor Screening Program, offered to participants free of charge, would include the following:

1. Completion by the participant of a family and personal history.
2. Height and weight.
3. Blood pressure and pulse check.
4. Rhythm strip (lead I).
5. Serum cholesterol.

6. Random blood sugar.

7. Counseling about possible risk factors.

8. Forwarding of test results to participants and to the family physician.

Because this was a co-sponsored program with the Maine Heart Association, Stephens Memorial Hospital agreed to provide the Program Coordinator, totally responsible for planning and implementing the project, as well as testing site for the program. In addition, the hospital processed the blood sugars and blood cholesterol and employed an additional technician for phlebotomy during the program. The Maine Heart Association in turn agreed to provide two employees to be on site for the duration of the program, electrocardiographic materials, and EKG interpretation by volunteer cardiologists. Compilation and mailing of test results to physicians and participants, as well as computer print-outs of the completed results of the screening, were provided by the Maine Heart Association.

## III. PROGRAM PLANNING AND PROMOTION:

A signed endorsement of support for the program and pledge to provide medical follow-up of any patient with problems was obtained from the physicians in the hospital service area. The Project Coordinator visited the Stephens Memorial Hospital Auxiliary, the Oxford Hills Health Council, the Nurses' Club, and the Androscoggin Home Health Agency to explain the Risk Factor Screening Clinic. These organizations agreed to provide professional and volunteers to assist with the program. Contacts were also made with the Central Maine General Hospital School of Nursing who agreed to provide three student nurses for three full days as a learning experience in community health education.

The twelve major industries in the hospital service area were contacted initially by a letter explaining the program, followed by a personal contact from the Program Coordinator. All industries agreed to allow their employees to participate in the screening by appointment during working hours without penalizing them for time lost. In deference to the gasoline shortage, they also agreed to transport employees to and from the site at the hospital. The Program Coordinator surveyed the 12 industries and figures indicated a work force of 2,200 people between the ages of 18 and 64, the age group thought most to benefit from the clinic. Expecting that possibly half that number would take advantage of the opportunity, it was decided to make the program available to

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1,500 people, including the general public who might also make appointments.

To accommodate 1,500 appointments, the program was planned to operate on two Saturdays from 8:00 a.m. to 4:00 p.m., five weekdays from 8:00 a.m. to 5:00 p.m. and five evenings from 6:00 p.m. to 8:00 p.m. Four people would be booked every 12 minutes. Industrial employees would be booked during the day hours, leaving evenings and Saturdays for the general public. Each assisting organization submitted a list of available volunteers to the Project Coordinator four weeks prior to the program. These people were contacted and scheduled for specific assignments during the program. The plan called for 300 volunteers; many volunteers, when contacted, offered to work more than one shift, thus reducing the necessary number of volunteers to 130 people.

The response from industrial employees was so great that nearly all 1,500 appointments were filled before appointments were offered to the public. The program was expanded three more days to allow for another 500 people. By May 11th, 1,800 appointments had been made and it was decided to allow walk-ins as long as it did not cause delays in meeting appointment times.

#### IV. PROGRAM IMPLEMENTATION:

The screening site was set up with teams of 16 volunteers each. Four volunteers registered participants and assisted them in filling out history sheets. This sheet accompanied the person through the screening and all available data was recorded on it. The sheet was a three-part form, one part to be sent to the participant, another to his physician and the final sheet was kept by the Maine Heart Association after all test results were recorded on it. From these sheets, data was fed to a computer which provided the final print-out of results. Two EKG machines were operated by volunteers who were taught to take a lead I EKG. Two volunteers measured height and weight. Two nurses took blood pressure and pulse and the laboratory technician drew blood samples which were labelled by another volunteer. Four health professionals counseled participants about known risk factors and explained the test results they would receive in the mail. The total cost to the hospital including salaries of one extra laboratory technician and overtime pay for regular laboratory technicians and supplies, reagents for tests, needles and tubes, etc., was figured at 88 cents per participant.

#### V. PROGRAM RESULTS:

Ultimately, 1,965 Oxford Hills area residents (ages 18-70) were screened and educated to the risk factors involved in coronary artery disease and hypertension. One hundred and thirty individuals donated 1,672 hours of volunteer time. Members of the Tri-County Health Planning Agency, i.e., Oxford, Androscoggin and Franklin counties visited the site during the screening. A

report was contained in their monthly newsletter. One person examined was found to have an extreme bradycardia. The same day she was referred to her family physician. The patient in turn was seen by a cardiologist and shortly thereafter a permanent pacemaker was inserted. Today this patient is gainfully employed with no loss of time due to her health.

The following are tabulated results of the risk factor screening clinic:

DIASTOLIC BLOOD PRESSURE VALUES		
<i>mm Hg</i>	<i>Classification</i>	<i># of participants *</i>
90-100	mild	307
100-120	moderate	57
120 & over	severe	5

BLOOD SUGARS (NON FASTING)	
<i>mg/dL</i>	<i># of participants *</i>
150-200	41
200-300	11
300 & over	4

CHOLESTEROL DETERMINATIONS (NON FASTING)		
<i>mg/dL</i>	<i>Classification</i>	<i># of participants *</i>
250-350	mild	469
350-500	moderate	36
500 & over	severe	2

#### ABNORMAL ELECTROCARDIOGRAPHIC CHANGES IN LEAD I

<i>Abnormality</i>	<i># of participants *</i>
Rhythm disturbances	26
ST & T wave abnormalities	57
Bundle Branch Block	34
Greater than normal R wave amplitude	41

\*Total number of participants screened was 1,965.

A copy of the results was sent to those physicians who had agreed to provide follow-up care. Physicians, however, were asked to forward their follow-up findings to Maine Heart Association in Augusta for further evaluation to the merits of this rather extensive screening.

#### VI. CONCLUSIONS:

The response of area residents to the program was gratifying and underscored the belief that people are concerned with preventive health care and education when it is presented to them conveniently and in a form they can afford. The coordination of all community health resources with a volunteer health agency proved the strength and value of joint efforts by producing unlimited amounts of manpower resources and expertise.

The success of such a program is very difficult to measure. Results from those examined and reported to their physicians has been most gratifying. Polling those involved in the organization and actual operation of this screening leads one to believe that further programs with regard to hypertension, diabetes, hypercholesterolemia and coronary artery disease would be both needed and well received here in the Oxford Hills area.

# Primary Malignant Lymphoma of Colon

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## INTRODUCTION

Involvement of different portions of gastrointestinal tract by malignant lymphoma has been reported in the literature, but cases of primary lymphoma of colon and appendix are rare.<sup>1,2</sup> The gastrointestinal tract may be involved in generalized lymphoma, but lymphomas localized to the gastrointestinal tract and regional lymph nodes should be the only ones considered, as primary lymphomas.<sup>7</sup> This represents one case of malignant lymphoma of the colon presenting interesting clinical, radiological and autopsy findings.

## CASE REPORT

A 44-year-old man was admitted to Stephens Memorial Hospital in December 1974 with the complaint of abdominal discomfort of a month's duration. He had been seen in the Emergency Room a week earlier with the same complaint. The discomfort was not relieved by analgesics or antacids. Gallbladder and G.I. barium meal studies revealed a functioning gallbladder and irritable duodenum. The patient had a past history of surgical correction for coarctation of the aorta and had been receiving Aldomet® for persistent hypertension.

On admission he appeared quite ill. The temperature was 98.0 F., pulse 80, and respirations 25. The blood pressure was 182/80 mm. Hg. No enlarged lymph nodes were found. On auscultation of the heart, a Grade III/VI pan-systolic murmur and an atrial gallop were heard. The liver and spleen were not palpable. No definite localization of tenderness or rebound tenderness was noted, although he complained of vague tenderness on the left side of the umbilicus. Peristalsis was present and the inguinal regions were normal.

The urine was normal. The hematocrit was 45%, white cell count was 5,800 with 22% bands, 31% segmented neutrophils, 29% lymphocytes and 18% monocytes. The red blood cells and platelets showed normal morphology. Serum amylase was 72 units (normal 60-160), and electrolytes were normal.

The glutamic-oxaloacetic transaminase (SGOT) was 55 and the alkaline phosphatase 2.9 Bodansky units (normal 1.5-5). The urea nitrogen was 17 mg., glucose 109 mg., uric acid 4.4 mg., creatinine 1.0 mg. and serum bilirubin 1.0 mg./100 ml. Chest radiograph was normal as well, except for rib-notching secondary to the coarctation. Radiographs of the abdomen demonstrated several loops of gas-filled small bowel with no distention, and no evidence of obstruction of free air. Intravenous pyelogram showed normal function and drainage bilaterally. Barium enema showed contraction of cecum which never fully distended, with a defect on the lateral aspect felt to be due to contraction rather than intrinsic mass (Fig. 1). The possibility of inflammatory disease was suggested. A barium meal repeated after three days showed the distal half of the duodenal loop to be in constant spasm with slight prominence of the mucosal folds (Fig. 2). The C-loop appeared widened, and the antrum, duodenal bulb and proximal loop of duodenum were elevated and partly effaced. Aldomet and Demerol® were administered during the first five days. On the sixth day, patient had no pain, but felt the sensation of abdominal fullness. A repeat barium enema showed an irritable lesion in the right cecum causing contraction and the ileum did not reflux well. Repeat barium meal on the eighth day showed widening of the loop and a double border in the lower part of the bulb and antrum. Physical examination at this time revealed a palpable mass in the epigastric region.



Fig. 1. Barium enema showing a filling defect in cecum.

Mild pancreatitis with possible pseudocyst formation was considered and surgical intervention at this stage was considered undesirable. Since his pain had subsided, the patient requested discharge from the hospital. It was decided that the patient would be readmitted for surgery after a month's convalescence. The patient died at home shortly after discharge.

## AUTOPSY FINDINGS

The cecal mass was well demarcated and polypoidal in configuration, projecting into the lumen of the cecum. The mucosal surface was ulcerated. On sectioning, a fleshy gray tumor infiltrating the wall of the cecum was noted. Histologically, the lesion was composed of immature pleomorphic reticulum cells with folded nuclei, prominent nucleoli and varying amounts of cytoplasm (Fig. 3). The liver and spleen were unremarkable. Regional lymph nodes were replaced by reticulum cell sarcoma. No other lymph nodes were involved. The right common iliac vein was surrounded by enlarged lymph nodes and showed unorganized thrombus. The mesentery and peripancreatic fat showed marked congestion, focal areas of hemorrhage and necrosis. Histologically, the peripancreatic fat contained lymphatic channels packed with reticulum cell sarcoma (Fig. 4). The pancreatic tissue showed unremarkable exocrine glands and islets. The immediate cause of death was an acute pulmonary embolus.

## DISCUSSION

Malignant lymphoma can involve the colon primarily as a localized entity or secondarily as man-

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Fig. 2. Barium meal showing widening of loop of duodenum.

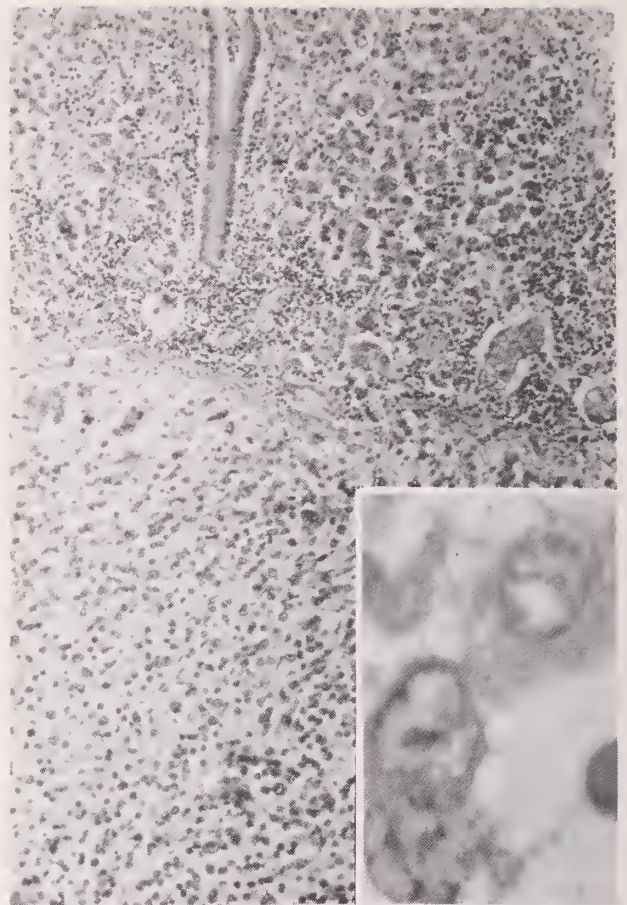


Fig. 3. Cross section of cecal wall showing immature pleomorphic reticulum cell sarcoma involving mucosa and submucosa. (Hematoxylin and Eosin Stain X 100. Inset X 1000)

ifestation of generalized lymphoma. For a lymphoid tumor to be regarded as primary in colon, it should meet the following criteria:<sup>7</sup>

1. There should be no generalized or palpable superficial lymphadenopathy.
2. Total and differential count should be in the normal range.
3. At laparotomy or autopsy, the bowel lesion should predominate in the lymph nodes draining the area — the only nodes obviously affected.
4. The liver and spleen should be free.

Our case meets all these requirements, excepting the differential count. The change noted in the pancreatic region showed lymphatic channels dilated and packed with reticulum cell sarcoma. The spleen and liver were not involved. The mesentery showed infiltration by reticulum cell sarcoma with extensive hemorrhage and edema.

Bush stresses that the involvement of mesentery alone is not sufficient to place a patient in this classification.<sup>6</sup>

In our case the mesenteric involvement was secondary to spread from the primary lesion in the cecum. The interesting part of this case was the localization of symptoms to epigastric region and radiological findings pointing to pathology in the pancreas. No other definite mass was palpable in the region of the cecum. No symptoms or signs of obstruction were noted.

Primary malignant lymphoma of the colon is rare; 0.5 to 1% of all malignant neoplasms of the colon are primary malignant lymphomas.<sup>1</sup> Glick, et al reviewed all case reports of lymphoma of the colon between 1905 to 1958 examined at the Mayo Clinic and found 27 cases which fulfilled the criteria of primary lymphoma.<sup>2</sup> Similarly, Ehrlich (1968), reviewed 323 patients who came to autopsy at Memorial and James Hospital, New York, during a 5-year period.<sup>3</sup> Colon was the site of involvement in 36 cases, and in 23 cases, lesion was due to tumor. The ratio of male to female is 2:1. Malignant colonic lymphomas have been reported in all age groups, but it is more common in childhood and in the sixth decade.

Primary lymphoma may either involve colon or rectum presenting as tumor with or without regional lymph node involvement, or it may show as multiple and diffuse polyposis of gastrointestinal tract.<sup>1,2,7</sup> Localized lesions may manifest in three forms: annular, protuberant growth or thickening with aneurysmal dilatation.

The right colon, particularly the cecum, is the most common site in the large bowel followed by rectum. This distribution has been attributed to the preponderance of lymphoid tissue in these areas.<sup>7</sup> In

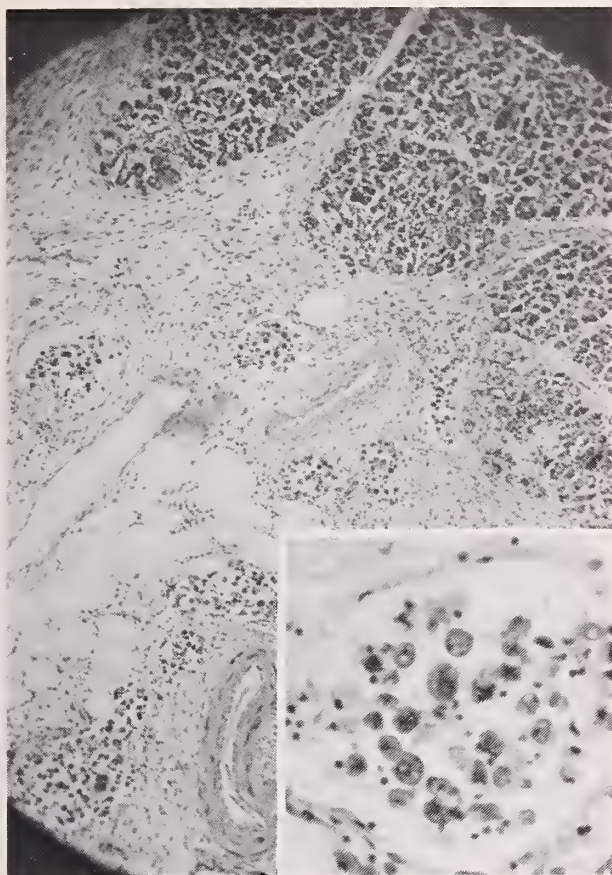


Fig. 4. Cross section of pancreas showing dilated lymphatics filled with reticulum cell sarcoma cells. (Hematoxylin and Eosin Stain X 100, Inset X 450)

about half the cases, regional lymph nodes were involved. Malignant lymphomas of the colon may show characteristics of one cell type or may show variable cytological pictures. Reticulum cell sarcoma and lymphosarcoma are equal in frequency. Wychulis reported reticulum cell in 6, lymphoblas-

tic 6, giant follicle 1, Hodgkin's and mixed 5.<sup>1</sup> Glick classified the 27 malignant lymphomas as lymphocytic 5, lymphoblastic 9, mixed cell 1, reticulum cell 11.<sup>2</sup> It has been reported that the type of lymphoma does not effect the survival except in the case of giant follicular lymphoma.

The patient's differential count was abnormal. In retrospect, the 18% monocytosis pointed to serious disease, as an absolute monocytosis always indicates.<sup>8</sup> In this patient, the monocytosis was secondary to the existence of (but not necessarily dissemination of) lymphoma.

### CONCLUSION

Correct diagnosis of primary lymphoma of the colon is made rarely prior to surgery because of varying gross configuration of the lesion with different x-ray findings.<sup>1</sup> Usually, radiological examination after barium enema reveals or indicates a neoplasm.<sup>5</sup> In our case, the changes in the duodenal loop overshadowed the lesion in the colon, causing us to focus on the pancreatic bed rather than on the site of the lesion.

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# Tubal Sterilization

## An Update of the Irving Technique

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### ABSTRACT

In a thirty-six month period, 257 women underwent tubal ligation, ninety-six of them in the postpartum period. The Irving technique was used in all cases. There were no serious complications and no failures. The overall complication rate was 3.5%. The average operating time was thirty-two minutes. The average hospital stay for the last fifty interim patients was 1.6 days. The hospital stay of the postpartum patient has not been prolonged.

### INTRODUCTION

In early 1971, the wife of a local physician underwent laparoscopic sterilization by an experienced colposcopist. An undetected cautery injury of the small bowel resulted in intra-abdominal sepsis which nearly cost her her life. In a community of less than 10,000 people, such a misfortune rapidly gains notoriety, and considerable pressure was brought to bear on the medical community to provide a satisfactory alternative form of sterilization. A review of the literature revealed general agreement that the most effective tubal ligations are the Irving and Uchida procedures.<sup>2</sup> Failures of either technique are rare; no percentages are recognized. On the other hand, laparoscopy is reported to fail at a rate of from 0.4%<sup>5</sup> to 2.8%.<sup>4</sup>

The morbid aspects of sterilization are a major concern in today's economy. For that reason, hysterectomy does not really enter into consideration, and is not a part of this study. Laparoscopic sterilization is commonly performed on a day care basis, and patients are seldom hospitalized more than twenty-four hours after the procedure.<sup>8</sup> In some series, the length of stay is longer, lasting up to little over three days.<sup>3,5</sup> Whereas, the length of stay after a tubal ligation might be up to eight days.<sup>3</sup> The complications of laparoscopic sterilization range from 3% to 8%.<sup>3,7</sup> The complications of open tubal ligations ranges up to 18.6%.<sup>3</sup>

It is of interest to note that in our small, semi-rural area, during the same time that 257 tubal ligations were performed, 140 vasectomies were done. This ratio of nearly two tubal sterilizations to each vasectomy is in direct contrast to the national ratio of three vasectomies to each female sterilization.<sup>6</sup>

### MATERIALS AND METHODS

The record of every patient undergoing tubal ligation from July 1973 through June 1976 was reviewed. Two hundred and fifty-seven records were

TABLE 1

AGE DISTRIBUTION OF PATIENTS IN STUDY	
Age	Number
Less than 22 yr.	14
23-27	83
28-32	73
33-37	50
38-42	30
Over 42 yr.	7

TABLE 2

TYPES OF SECOND PROCEDURES PERFORMED WITH SAME ANESTHETIC

Procedure	Number
Oophorectomy, partial or total	7
D & C	6
Myomectomy	4
Appendectomy	4
Uterine suspension	3
Cautery cone of cervix	3
Preperitoneal herniorrhaphy	2
Posterior perineorrhaphy	1
Plastic repair of abdominal wall	1
Saphenous vein stripping	1

studied. Eighty-three tubal ligations were done within 48 hours of delivery, 13 more with caesarean sections, and five more with elective abortions. The patients ranged in age from seventeen to forty-eight, with an average of 30.8 years. The ages are more specifically broken down in Table 1. Parity ranged from 0 to eleven, with an average of 3.2. Thirty-two patients had second procedures performed under the same anesthetic. These are outlined in Table 2. All patients were interviewed in depth in the office, usually with their husbands before scheduling. For the last year, as a result of patient pressure, patients who live locally are being admitted to the hospital on the morning of their operation. They have undergone examination, anesthesia interview, chest x-ray, laboratory urinalysis and hemogram, and surgical prep the day prior to their admission. They have been given written instructions that define, in plain English, the meaning of 'NPO since midnight.' If they are to be done in the postpartum state, they are scheduled within 48 hours of delivery.

Under general anesthetic, the interim patient is placed in ten degrees of Trendelenburg position, and the abdomen is entered through a Pfannenstiel incision which ranges in length from three to eight cm., depending on the obesity of the patient. The incision will be lengthened by two or three cm. if a uterine suspension, myomectomy or preperitoneal herniorrhaphy is to be performed. The postpartum patient is explored through a three to five cm. infra-

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umbilical incision. The Fallopian tube is grasped with Babcock forceps, and the fimbriated end is positively identified. There is a very constant blood vessel which ascends through the mesosalpinx approximately 3 cm. from the uterine cornu. The mesosalpinx is fenestrated on either side of this vessel, which is then clipped with a medium tantalum clip. A centimeter of the Fallopian tube is removed between tantalum clips laterally, and a chromic ligature medially. Now, either the cut end of the tube is drawn into a tunnel made in the myometrium with cautery, in the fashion of the Irving technique, or the leaves of the broad ligament are separated to expose the posterior aspect of the round ligament, and the ligature is passed through the round ligament and tied anteriorly. The latter procedure is most likely to be followed in the postpartum patient because of the bulkiness and vascularity of the uterus. The ever-present edema of the tissues actually makes the dissection more easy. The peritoneum and fascia are closed in the usual fashion, and a subcuticular suture of fine absorbable material is used to close the skin. The patient is then allowed activity, diet, and discharge home at her discretion. All patients were seen again after four to six weeks for examination of the integrity of the wound, and at the same time interviewed in respect to the length of time it took to return to activities of daily living and/or usual employment.

### RESULTS

All 257 patients were followed as outlined above. There were a total of nine postoperative complications, for an occurrence rate of 3.5%. They are outlined in Table 3. Except for the patients with atelectasis as documented by abnormal physical findings and/or positive chest roentgenograms, no patient had more than one degree of temperature elevation. No patient required narcotics after the first twenty-four hours, with the exception of the woman with the unexplained abdominal pain, and she was comfortable when discharged after forty-eight hours. The average operating time for those patients undergoing sterilization alone was 32 minutes, with a range of fifteen to forty-five minutes.

In our hospital, two-thirds of the postpartum patients go home on the third postpartum day. The remainder go home on the fourth day after delivery. The average caesarean section patient stays five days. With these figures in mind, no patient on the obstetrical service who underwent tubal ligation had any prolongation of her normal hospital stay. Without exception, those women who underwent termination of pregnancy left the hospital twenty-four hours later.

As I stated above, our patients were the instigators of the 'same day admission.' It is our policy to let them decide for themselves when they would like to be discharged. Of course, they must be afebrile, their wounds must show no induration or erythema, they must be eating a regular diet, and

TABLE 3

COMPLICATIONS	
Type	Number
Atelectasis	3
Urinary tract infection	1
Superficial wound infection	2
Superficial wound hematoma	1
Excessive abdominal pain	1

comfortable activity must have been noted by the nurses. Our last fifty interim patients have been 'same day' admissions. Their total hospital stay has averaged 1.6 days. No patient has been discharged home with a prescription for narcotic analgesics; nor have we had requests later for such drugs.

At the time of final visit, all wounds have been perfectly healed, including those which were previously infected, and the one in which a hematoma formed. Virtually every housewife was back to her 'chores' on a full-time basis within five days of her operation. The women with clerical jobs were back to work within ten days; some as early as five days. The average industrial worker was out of work for two weeks, with the longest period of unemployment lasting three weeks.

### CONCLUSIONS

By modifying the Irving technique, but adhering to the principle of seeking a serosal cover to the medial portion of the tube, it has been possible to perform this highly successful tubal ligation through very small abdominal incisions. It is also now possible to do the same procedure on the postpartum uterus. It can be done swiftly with an acceptable number of postoperative complications. The total morbidity of the procedure will likely never reach the low level achieved by laparoscopic sterilization, but the truly hazardous complications of the latter are avoided. The morbidity is very much less than that found with hysterectomy, thus improving greatly the cost-effectiveness of the procedure. We have done one hundred of these procedures in the last twelve months; so it would appear that a certain measure of satisfaction and confidence has been restored in our populace.

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*Continued on Page 146*

## Pharmacotherapy of Parkinson's Disease

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### ABSTRACT

Parkinson's disease has proven to be considerably more complex than was initially postulated. While it has been clear for some time that the nigro-striatal dopamine-acetylcholine system is probably the central element in the pathogenesis of Parkinson's disease, it has only recently been appreciated that other putative neurotransmitters of the basal ganglia (norepinephrine, histamine, serotonin, gamma amino butyric acid) at least modulate the symptoms of Parkinsonism.

The pharmacologic management of Parkinson's disease is presently limited primarily to manipulation of the dopamine-acetylcholine system. Levodopa, with or without a peripheral dopa decarboxylase inhibitor, is the current drug of choice in the management of idiopathic and post-encephalitic Parkinson's disease. Modification of the serotonin-histamine system via the use of antihistamines may be useful in some patients. There are also many adjunctive agents which may be employed in combination with or in place of levodopa. Levodopa clearly has no place in the treatment of neuroleptic-induced Parkinson's disease. Anticholinergics and antihistamines are the agents of choice.

### ABBREVIATIONS

CNS — Central nervous system  
DA — Dopamine  
NE — Norepinephrine  
Ach — Acetylcholine  
GABA — Gamma amino butyric acid  
Cyclic AMP — Cyclic adenosine monophosphate

One of the major causes of neurological disability in the elderly is Parkinson's disease. It is readily recognizable by most clinicians and consists of the clinical tetrad of akinesia (poverty of spontaneous movements, "mask-like" facies), rigidity of muscular tone, a characteristic tremor in repose, and an aberration of postural mechanisms (flexed position

of stance, difficulty in turning and the characteristic festinating, hurried gait). Since the original clinical description of the syndrome by James Parkinson in 1817, numerous clinical and pathological observations have been made. However, it was not until sophisticated biochemical assays and histochemical techniques were developed that we were able to comprehend, albeit in an imperfect way, the pathophysiology of Parkinson's disease.

This review will be concerned with idiopathic, post-encephalitic, and drug-induced Parkinsonism. These conditions account for the vast majority of patients with Parkinsonism. The review will not cover the syndromes produced by carbon monoxide and manganese toxicity nor the disputed condition referred to as "arteriosclerotic Parkinsonism."

### PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

A neurotransmitter is a substance which is produced by neurons. It is transported along the axons of these cells and is released at a distant location to influence the discharge of other neurons. Since 1954, a number of substances have been identified as definite participants in neuronal transmission. They include Ach, DA, NE, serotonin and GABA. Other substances which may function as neurotransmitters include histamine, cyclic-AMP, glutamic acid and "substance 'P'."

In order to comprehend Parkinson's disease, a rudimentary knowledge of the anatomy of the extrapyramidal system and, more specifically, the basal ganglia is needed (Figure 1). In addition to its other functions, the extrapyramidal system maintains posture and muscle tone and modulates voluntary movement. The portions of the extrapyramidal system involved in Parkinson's disease include the caudate nucleus and the putamen (referred to collectively as the neostriatum), the globus pallidus (which receives fibers from the neostriatum), and the substantia nigra (which is located more inferiorly in the midbrain and projects its dopaminergic fibers to the neostriatum and globus pallidus). When the aforementioned structures are considered collectively, they are known as the basal ganglia.

After the basic structure and function of the nigro-striatal DA-containing neuronal system was demonstrated in 1964, the pathophysiology of Parkinson's disease appeared rather straightforward: lesions in the substantia nigra decimate cell bodies in the nigrostriatal tract that utilize DA as a neurotransmitter, creating a "transmitter imbalance" with a lack of DA and a functional excess of Ach.

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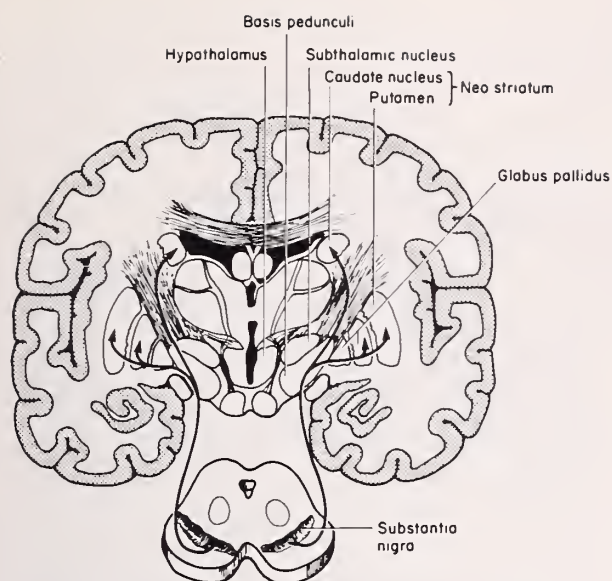


Fig. 1. Schematic drawing of the extrapyramidal system.

This hypothesis, however, provided only a partial explanation of the pathophysiology of Parkinson's disease.<sup>1</sup>

In order to give the reader a better understanding of the complex biochemical milieu at the basal ganglia, a brief review of the known neurotransmitter systems will now be presented. Several excellent review articles on neurochemistry are available and the reader is referred to them for a more detailed description of transmitter synthesis, storage, and metabolism.<sup>2,3</sup>

The cholinergic system has a widespread distribution in the CNS and with few notable exceptions, it is predominantly excitatory (as it is in the periphery). This excitation can be associated with what is generally referred to as the "positive" symptoms of Parkinson's disease, e.g., tremor. The direct injection of Ach into the globus pallidus of Parkinsonian patients during stereotactic procedures increases tremor activity contralaterally while injection of anticholinergics brings about a diminution of the tremor.<sup>4</sup> Since the striatum contains the highest concentration of Ach in the CNS, it appears likely that a relative cholinergic dominance plays some role in the symptomatology of Parkinson's disease.

Monoamines active in the CNS include serotonin and the catecholamines dopamine and norepinephrine. All three transmitters are present in subnormal amounts in the brain tissue of Parkinsonian patients, but the changes in NE and serotonin are slight when compared to DA. Although both DA and NE are found throughout the CNS, there are marked regional variations in their concentrations and fairly specific, identifiable functional pathways. The caudate nucleus (see Figure 1) contains, for example, almost one hundred times as much DA as NE.

The highly divergent nor-adrenergic system is believed to be involved in the pathophysiology of Par-

kinson's disease. This belief is based, in part, on the observation that the only consistent pathology in Parkinsonian patients, aside from degeneration in the substantia nigra, is degenerative changes in the locus coeruleus — the largest group of nor-adrenergic cell bodies in the CNS.<sup>5</sup>

By and large, the NE system causes post-synaptic inhibition at receptor sites at which it is functional. This inhibition may initially appear to be paradoxical since drugs like amphetamine that cause increased release and decreased re-uptake of NE evoke behavioral excitement. A possible explanation is that the nor-adrenergic system acts predominantly at inhibitory centers producing inhibition of these centers or "disinhibition." Eugene Roberts<sup>6</sup> and others have written extensively on the concept of disinhibition as an architectural principle of the nervous system.

The dopaminergic system has a much more limited projection than the nor-adrenergic system.<sup>5</sup> The most important pathway involves cells originating in the substantia nigra that have axonal projections to the neo-striatum and globus pallidus (Figure 1). This dopaminergic pathway can be demonstrated in animals by electrically stimulating the substantia nigra and measuring DA concentrations in the striatum. The DA is manufactured in the substantia nigra and is transported via axonal flow to the striatum where it acts as a transmitter. Interruption of this nigro-striatal pathway will markedly diminish the concentration of DA in both the caudate and putamen; and this is in fact what occurs in Parkinson's disease. Often at necropsy, no DA is found in the striatum. The rationale for levodopa therapy is based upon this deficiency of DA at the striatal receptors.

Released DA apparently acts predominantly as an inhibitory synaptic transmitter. A current theory conceptualizes the dopaminergic system as consisting of two separate populations of DA receptors: the classical inhibitory DA receptors ( $D_1$ ) and a separate population of receptors that are facilitative in response to DA ( $D_2$  receptors).<sup>7</sup> In an environment of relative DA deficiency, the hypostimulated  $D_1$  receptors would be responsible for many of the classic Parkinson's symptoms while hypostimulation of the  $D_2$  receptors results in no apparent effect. In the situation of relative DA excess, hyperstimulation of  $D_2$  receptors would result in the classic spectrum of adventitious movements seen in levodopa dyskinesia, while overstimulation of the  $D_1$  receptors would result in no apparent effect.<sup>7,8</sup> This theory provides an explanation for the relief of parkinsonian symptoms without the appearance of dyskinesic movements in some levodopa-treated patients while other patients exhibit disabling dyskinesias without any diminution of parkinsonian symptoms. The single DA receptor theory fails to explain those conflicting observations.

Many functions in the CNS have been attributed to serotonin, but it is not yet clear what specific effect it exerts aside from a general depressant effect

on behavioral activity.<sup>9</sup> In animal experiments, serotonin has been shown to relieve tremor caused by experimentally-induced lesions in the mid-brain.<sup>10</sup> However, in the treatment of Parkinson's disease, therapy with serotonin or its precursors has been disappointing. The serotonin system may have a role in Parkinsonism since serotonin levels are consistently decreased in these patients. Whether this is a significant finding or a nonspecific effect of dopaminergic depletion remains to be elucidated. Further credence to the theory that serotonin may at least modify the symptoms of Parkinson's disease is provided by the observation that many antihistamines show beneficial effects on Parkinsonian symptoms, particularly the tremor.<sup>7,11</sup> These effects appear to be out of proportion to their anticholinergic activity and may be due to their re-establishing a balance in the serotonin-histamine system.

Recent work has revealed a striato-nigral pathway which utilizes GABA as a neurotransmitter.<sup>12,13</sup> The highest concentration of GABA in the brain is found in the substantia nigra with the striato-nigral pathway transporting the GABA inferiorly. This system appears to inhibit dopaminergic neurons in the substantia nigra. Whether this system plays a role in either Parkinson's disease or the rate striatonigral degenerations which mimic Parkinson's disease is not known.

Symptoms of Parkinson's disease may be transiently induced by drugs that cause a relative CNS dopaminergic deficiency. Two separate mechanisms may be involved: (1) the depletion of DA from intraneuronal stores, or (2) the rendering of the DA receptor less sensitive to the effects of DA (Figure 2). Examples of agents in the former category include reserpine and tetrabenazine (an investigational drug in the United States used in the treatment of tardive dyskinesias). Parkinsonian symptoms induced by these drugs are readily reversible with exogenous levodopa since the underlying problem is one of a quantitative lack of DA.<sup>7,8</sup>

Among the drugs that render the dopaminergic receptor less sensitive to DA are the neuroleptic agents<sup>7</sup> such as the butyrophenones (e.g., haloperidol), thioxanthenes (e.g., thiothixene, chlorprothixene), dibenzodiazepines (e.g., clozapine), and many of the phenothiazines (e.g., chlorpromazine, perphenazine, trifluoperazine). Janssen<sup>14</sup> demonstrated that these agents form a mono-layer coat over a dose-dependent portion of DA receptors, thus forming a physical barrier between the DA and its receptor. Administration of exogenous levodopa does not reverse the parkinsonian symptoms induced by these agents since reduced sensitivity of the DA receptor, rather than reduced amounts of DA, is responsible for the symptoms.<sup>7,8,15</sup> The incidence of drug-induced Parkinson's disease varies widely among the various neuroleptic agents and appears to be affected by their anticholinergic activity. Agents with little or no anticholinergic activity (e.g., haloperidol,

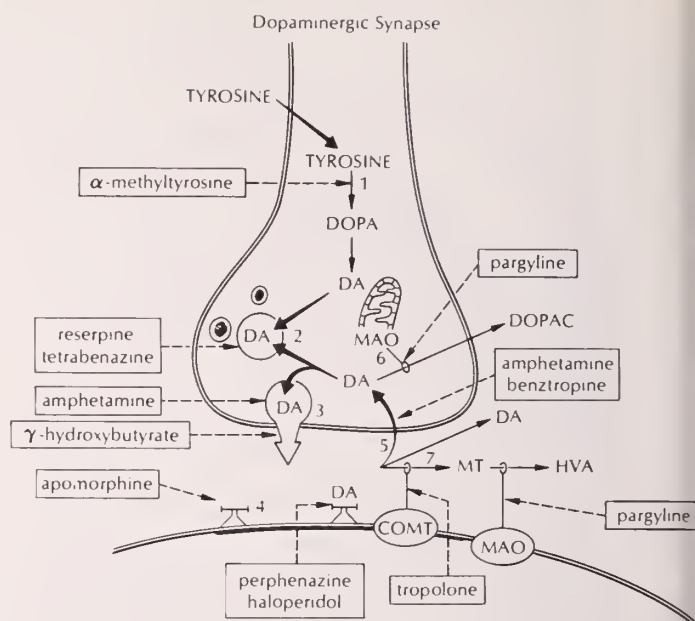


Fig. 2. Schematic model of a central dopaminergic neuron indicating possible sites of drug action.

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trifluoperazine, fluphenazine) routinely cause drug-induced Parkinson's disease, whereas agents that are strongly anticholinergic (e.g., thioridazine, mesoridazine, clozapine) rarely cause such symptoms.<sup>8,16</sup>

In drug-induced Parkinson's disease, the predominant symptoms are akinesia and rigidity; tremor is usually less prominent.<sup>8</sup> The symptoms are generally reversible upon discontinuation of the offending agent but often remit, even with continued therapy.<sup>7,8</sup> Acute dyskinetic reactions usually respond rapidly to parenteral administration of a central anticholinergic such as benzotropine (Cogentin®) or diphenhydramine (Benadryl®).

## PHARMACOTHERAPY

Since the primary neurotransmitter imbalance in parkinsonism involves a relative deficiency of DA and a relative excess of Ach, treatment of Parkinson's disease is primarily limited to pharmacologic manipulations of the DA-Ach system. Other neurotransmitters may modulate the symptoms of Parkinson's disease,<sup>8</sup> but they appear to be of secondary importance.

## ANTICHOLINERGIC THERAPY

The anticholinergics are the oldest preparations used in the treatment of Parkinson's disease. Tincture of belladonna has been used for over 100 years. The newer synthetic compounds (see Table I) are more appealing from a number of standpoints.

The ideal anticholinergic drug would have marked central and little or no peripheral effect and preferably act only at the striatum. Unfortunately, even the first condition cannot presently be met. The relative

TABLE 1

ANTICHOLINERGIC AGENTS USED IN PARKINSON'S DISEASE	
Drug	Usual Dose
<i>Naturally Occurring Alkaloids</i>	
Atropine	100-250 $\mu$ g four times daily
Scopolamine (Hyoscine)	300-100 $\mu$ g three to four times daily
<i>Synthetic Anticholinergics</i>	
Trihexyphenidyl (Artane, <sup>®</sup> Tremin, <sup>®</sup> Pipanol)	2-4 mg three times daily
Procyclidine (Kemadrin <sup>®</sup> )	2.5-10 mg three times daily
Biperiden (Akineton <sup>®</sup> )	2 mg three to four times daily
Cycrimine (Pagitane <sup>®</sup> )	2.5-5 mg three times daily
<i>Antihistamines</i>	
Diphenhydramine (Benadryl <sup>®</sup> )	25-50 mg three to four times daily
Orphenadrine (Norflex, <sup>®</sup> Disipal <sup>®</sup> )	50-100 mg three times daily
Chlorphenoxamine (Phenoxene)	50 mg three times daily
<i>Synthetic Anticholinergic-Antihistamines</i>	
Benztropine (Cogentin)	1-4 mg twice daily
<i>Phenothiazines</i>	
Promethazine (Phenergan <sup>®</sup> )	6.25-25 mg one to three times daily
Ethopropazine (Parsidol, Profenamine)	10-100 mg four times daily

ineffectiveness of the anticholinergics is probably related to two factors: (1) their general inability to reverse the essential pathology, and (2) their central and peripheral side effects. The most bothersome side effects are probably the central effects; they include delusions, hallucinations, somnolence, ataxia, and dysarthria. However, the peripheral effects of dry mouth, blurred vision, constipation, urinary retention, and tachycardia are hardly insignificant.

There are five major categories of anticholinergic drugs used in the treatment of Parkinson's disease (see Table 1). These include the naturally occurring alkaloids (e.g., scopolamine, atropine), the synthetic anticholinergics (e.g., trihexyphenidyl, procyclidine, biperiden, cycrimine), the antihistamines (e.g., diphenhydramine, orphenadrine, chlorphenoxamine), the synthetic anticholinergic-antihistamines (e.g., benztropine), and, paradoxically, a few phenothiazines (e.g., promethazine, ethopropazine).

Although the anticholinergics are no longer drugs of choice in the management of Parkinson's disease, certain indications for their use remain. They may be used in mild cases where the severity of the disease does not warrant the risks or demands of levodopa therapy upon the patient. They may also be used as adjunctive therapy in patients who tolerate levodopa poorly or as the sole drug in patients who cannot tolerate it at all. Some investigators believe that anticholinergic drugs have a synergistic effect when administered with levodopa; aside from diminishing the cholinergic striatal effects, anticholinergics may inhibit the reuptake and storage of dopamine at the striatum.<sup>11,17</sup>

In general, anticholinergic drugs rarely produce more than a 20% improvement and despite continued use, the symptoms tend to progress. This rather small rate of improvement is not surprising when one considers that cholinergic dominance does not appear to be primary in the pathogenesis of Parkinson's disease but rather appears to modulate

the effects of an already present DA deficiency. This is borne out by the observation that symptoms of Parkinson's disease cannot be induced in non-parkinsonian patients treated with a central cholinergic agent (e.g., physostigmine). Also, in untreated parkinsonian patients only the symptoms already present appear to be exacerbated by physostigmine; no new symptoms appear.<sup>7</sup> If DA deficiency were the only prerequisite for the appearance of cholinergic-mediated parkinsonian symptoms and if levodopa were to replace the deficient dopamine store, then one would expect to observe no effect when physostigmine is administered to Parkinson's patients chronically treated with levodopa. This has not been a consistent observation. Patients on long-term levodopa therapy who are given intravenous physostigmine and respond with a marked exacerbation of their parkinsonian symptoms (positive physostigmine test) routinely benefit from the addition of an anticholinergic agent to their regimen. Conversely, the parkinsonian patients on long-term levodopa therapy who demonstrate negative physostigmine test (exhibit little or no exacerbation of their Parkinson's symptoms when administered intravenous physostigmine) usually receive little benefit from the addition of an anticholinergic agent.<sup>18</sup>

Of the available anticholinergic agents, no one agent is consistently superior to the others. The antihistamines, however, are generally better tolerated in the elderly and may produce slightly greater relief from tremor.<sup>11</sup>

#### DOPAMINERGIC THERAPY

Several pharmacologic manipulations may be used in an attempt to correct the dopaminergic deficiency at the striatum. These are: (1) augmentation of the synthesis of brain DA, (2) direct stimulation of the DA receptors, (3) stimulation of DA release from pre-synaptic sites, (4) decreasing reuptake of dopamine by pre-synaptic sites, and (5) decreasing DA catabolism.

## *Augmentation of Dopamine Synthesis-Levodopa Therapy*

DA does not cross the blood-brain barrier for reasons that are not entirely clear, but dopa, its amino acid precursor, does. Since the initial clinical trials of high dose oral levodopa by Cotzias<sup>19</sup> and others in 1967, this drug has become the bulwark of therapy in Parkinson's disease.

Levodopa (Larodopa,<sup>®</sup> Bendopa,<sup>®</sup> Dopar<sup>®</sup>) therapy is associated with a number of problems that are primarily related to the drug's pharmacology. Levodopa is a relatively inert substance. It is metabolized to DA by L-aromatic amino acid (dopa) decarboxylase which is an ubiquitous enzyme both centrally and peripherally. Thus, most of an oral dose of levodopa is peripherally metabolized to DA, which does not cross the blood-brain barrier. The formed DA, as well as the other metabolites of levodopa (norepinephrine, epinephrine), has potent peripheral effects (cardiac arrhythmias, severe nausea and vomiting) that can severely limit the dose of levodopa. If peripheral dopa decarboxylase could be inhibited without affecting central dopa decarboxylase, the amount of dopa reaching brain receptors could be maximized and the peripheral side effects could be minimized. This has recently been accomplished with carbidopa and benserazide.<sup>11,20,21</sup>

One of the most common side effects of levodopa therapy is gastric upset with nausea and vomiting. This appears to be the result of two factors: direct gastrointestinal irritation and stimulation of the medullary emetic zone (area postrema). The area postrema has DA receptors identical to those in the striatum but the area postrema lies outside the blood-brain barrier.<sup>22</sup> High circulating levels of DA tend to activate these receptors, resulting in nausea and vomiting. One of the most dramatic effects of combining levodopa with a peripheral decarboxylase inhibitor (e.g., Sinemet<sup>®</sup>) has been a significant decrease in the incidence and severity of nausea and vomiting.<sup>20,23,24</sup>

Since combination therapy permits a 75-80% reduction of the dosage of levodopa, the risk of cardiac arrhythmias is reduced. In addition, it appears that at maximum tolerated dosage, the patients are clinically better with the addition of a decarboxylase inhibitor.<sup>20,24</sup> The other advantages are a smoother, more rapid induction phase of therapy and obviation of the drug interaction with pyridoxine (vitamin B<sub>6</sub>).

When levodopa is administered without the benefit of a peripheral decarboxylase inhibitor, concomitant administration of pyridoxine (a coenzyme for dopa decarboxylase) causes a significant increase in peripheral metabolism of the levodopa and, therefore, a marked decrease in the amount of levodopa that is available centrally.<sup>25</sup> When peripheral dopa decarboxylation is blocked with an agent such as carbidopa, the pyridoxine effect on peripheral levodopa metabolism is negligible.

The only real disadvantage of combination

therapy is the more rapid and perhaps slightly more frequent appearance of abnormal involuntary movements. This may be because many patients were never able to achieve sufficient intracerebral concentrations of DA to produce these movements since nausea and vomiting or other peripheral side effects usually intervened.<sup>7,8</sup>

Levodopa-induced dyskinesia is the ultimate dose-limiting factor. Commonly observed levodopa-induced dyskinesias include oral-facial dyskinesias, bobbing and turning movements of the head, and choreoathetoid movements of the limbs and trunk.<sup>11</sup> The dyskinesias appear to be related not to the severity or duration of the disease but to the dosage and duration of therapy.<sup>7</sup> The dosage that will produce dyskinesias is fairly constant for any given patient. Reducing the dosage usually will eliminate these unwanted effects, but will result in increased parkinsonian symptoms.

Two theories have been advanced for the cause of levodopa-induced dyskinesias. The first suggests an effect of DA on supersensitive denervated striatal receptors.<sup>8</sup> The second is based on the aforementioned theory that there are two populations of striatal DA receptors: one stimulated by DA (the D<sub>1</sub> receptors) and the other inhibited by DA (D<sub>2</sub> receptors). The relative sensitivities of these two populations of receptors would dictate which effect predominates.

Prolonged DA deficiency and its attendant neuronal degeneration may result in decreased responsiveness to exogenous levodopa. This theory is substantiated by the observations that the symptoms of Parkinson's disease usually do not progress during the first two years of therapy and that patients with longstanding, untreated disease are consistently among the poorest responders to levodopa therapy.<sup>7,15</sup> It seems reasonable then to initiate levodopa therapy early in the course of Parkinson's disease rather than to withhold therapy until the symptoms become severe since long-term use of levodopa may prevent the development of irreversible degeneration of the DA receptors. This is not to imply that chronic administration of levodopa stops or reverses the pathological changes of parkinsonism within the substantia nigra; there is no evidence to substantiate this.<sup>7,15</sup>

*Induction Phase of Therapy.* Parkinsonian patients not previously treated with levodopa should be started on combination therapy with Sinemet. Sinemet is available in a fixed ratio of one part carbidopa and ten parts levodopa, either 10/100 mg or 25/250 mg. Carbidopa in a dose of 70-100 mg/day will inhibit the majority of peripheral dopa decarboxylase. Higher doses have no apparent utility or toxicity. The usual starting dosage is one 10/100 mg Sinemet tablet thrice daily and is increased by one tablet every day or every other day until six tablets per day are reached. Above this dosage, 25/250 mg tablets can be used. Further titration can be made with either 10/100 mg tablets or levodopa alone. One

of the advantages of combination therapy is said to be the ease of administration. Many patients reportedly do well on thrice daily dosing while avoiding the moderate fluctuations in performance throughout the day that are common with levodopa alone. In our experience, dosing every three or four hours provides a more uniform response than dosing three or four times daily.

If a patient is responding well to levodopa without appreciable side effects, nothing is gained by switching to Sinemet. If, however, the response is less than optimal and the patient is continually inconvenienced by side effects, transfer can be accomplished without interruption. The usual daily schedule should be completed, omitting the evening doses of levodopa. The next morning, Sinemet should be started at approximately 20-25% of the former levodopa dosage.

*Maintenance Phase of Therapy.* Minor adjustments in dosage may be needed in order to conform to diurnal fluctuations or new-found activities in a once disabled patient. After a period of time the frequency of these variations in performance may increase.<sup>26</sup> They may take the form of good periods (usually in the morning and early evening) alternating with bad periods (usually in the afternoon and late evening), good periods alternating with dyskinesias, or even bad periods alternating with dyskinesias. Often these fluctuations respond to changes in the dosage schedule but the latter may indicate an overdosage.

Some patients, who appear to be responding quite well to levodopa, will suddenly experience a state of akinesia, masked facies, and stooped posture. This state may rapidly alternate with a phase of dyskinesic movements. This constellation of symptoms is often referred to as the "on-off" phenomenon. It is usually observed only after prolonged levodopa therapy, is most common in patients with advanced disease, and is not seen in untreated patients. The phenomenon can occur within seconds, continue for minutes or hours, and then remit. It may occur less often with combination therapy,<sup>27</sup> but this is not established. A number of therapeutic measures can be attempted.<sup>27</sup> They include increasing or decreasing the dosage, temporarily discontinuing the levodopa, adding an adjunctive medication, or placing the patient on a low protein diet (other aromatic amino acids may compete for the same absorption mechanism in the small bowel). There is increasing evidence that many of the paradoxical phenomena may be due to the loss of DA storage capability of the remaining nigral neurons. This could account for an exaggerated initial response to exogenous DA (the "on" portion) followed by a much shorter duration of action (the "off" portion).<sup>29</sup>

*Side Effects.* Dyskinesias, cardiac arrhythmias and gastrointestinal symptoms have already been discussed. Other commonly encountered side effects include mental disturbances (hypomania, delusions, hallucinations) and postural hypotension.

These effects may occur in up to 25% of patients treated with levodopa (with or without carbidopa). Postural hypotension may appear to be paradoxical since metabolism of levodopa yields DA, NE, and epinephrine, all of which are potent peripheral pressor agents. The peripheral activity of these metabolites may be offset by the central alpha-adrenergic agonist activity of DA and NE, resulting in a significant degree of centrally-induced hypotension.<sup>30,31</sup> If the observed hypotension were primarily of central origin, its incidence and severity would be expected either to increase or to remain the same with the addition of a peripheral dopa decarboxylase inhibitor and to decrease dramatically with the addition of a central dopa decarboxylase inhibitor. This appears to be the case.<sup>30,32</sup>

Some parkinsonian patients experience severe and persistent orthostatic hypotension while deriving marked benefit from levodopa therapy. In those whose medical status does not preclude the use of mineralocorticoids, treatment with oral fludrocortisone acetate, 0.05 to 0.2 mg daily, may be of significant value in reducing the degree of hypotension.<sup>30</sup> Alternatively, oral ephedrine in doses of 25 mg thrice daily and/or elastic stockings are often beneficial in reducing or abolishing the orthostatic hypotension.

If there is a question as to whether the patient will be able to tolerate any of the side effects of levodopa, he or she should be hospitalized for the first one or two days of therapy.

*Drug Interactions.* Phenytoin, when administered to patients who are well controlled on levodopa, appears to diminish the therapeutic effects of the levodopa. The mechanism is unclear.<sup>33</sup>

Reserpine and the neuroleptics should generally not be given to patients being treated with levodopa<sup>21</sup> since they may deplete interneuronal DA stores or effect a blockade of the DA receptors.

Alpha-methyldopa exhibits a weak blocking effect on dopa decarboxylase but, unlike carbidopa, it appears to work centrally as well as peripherally in therapeutic doses. As a result, its effects on levodopa are quite unpredictable: antagonism<sup>21,34</sup> as well as synergism<sup>21,35</sup> have been reported.

The monoamine oxidase inhibitors and pyridoxine can also interact significantly with levodopa. These interactions are covered elsewhere in this article.

*Contraindications.* Levodopa should be used with extreme caution, if at all, in patients with a significant degree of angina pectoris or severe cardiovascular occlusive disease where moderate to severe hypotension may precipitate myocardial infarction. Similarly, it should be avoided in patients with transient cerebral ischemic attacks. It is relatively contraindicated in patients with a history of major affective disorders and in patients with a history of or predisposition to malignant melanoma since levodopa is both a precursor to melanin and a stimulant to growth hormone release.<sup>11,15,36</sup> Levo-

dopa is relatively contraindicated in patients with a history of hemolytic anemia or G-6-PD deficiency.<sup>11</sup>

### *Direct Stimulation of DA Receptors*

Drugs that act by directly stimulating the DA receptors are not yet marketed in the United States, although several are currently undergoing clinical trials. The advantage of such a drug is that it has an effect independent of striatonigral degeneration, while the efficacy of levodopa depends on the ability of the remaining striatonigral neurons to decarboxylate levodopa to dopamine.

Among those drugs that act predominantly at the DA receptor, the most promising is bromocriptine, an ergot derivative.<sup>37,38</sup> Recently completed trials in the United States have shown that bromocriptine may be nearly as effective as levodopa with similar side effects.<sup>39,40</sup> has a significantly longer half-life than levodopa (6-8 hours versus 2-4 hours),<sup>40,41</sup> and may be especially useful in patients with tremor.<sup>39-41</sup> It is also effective in severely affected patients when levodopa is not,<sup>40,42</sup> and is an effective adjunctive agent when given in combination with levodopa or levodopa-carbidopa.<sup>41</sup> Apomorphine, a semi-synthetic derivative of morphine, has been utilized experimentally with good results. However, it has a rather short duration of action, possesses rather marked emetic properties, and can cause a significant degree of azotemia.<sup>43</sup> Recently, Cotzias and co-workers<sup>43</sup> have employed an apomorphine analog, N-propylnorapomorphine, with favorable initial results, most notably a decrease in the severity of the azotemia.

Lergotriple, a presumed DA receptor stimulating agent, appears to be effective in alleviating tremor,<sup>44</sup> but apparently does little to improve other clinical manifestations of Parkinson's disease. Preliminary data suggested that another agent, piribedil (ET-495), suffered from the same therapeutic limitations as lergotriple, but recent studies suggest that it may produce significant improvement when used adjunctively with levodopa.<sup>45</sup>

### *Stimulation of Dopamine Release*

Amphetamine may produce a mild degree of benefit if the prominent symptom is akinesia. It can, however, markedly exacerbate a tremor and should be used judiciously. Studies by Birkmayer and others strongly suggest that the central action of dextro-amphetamine is indirect, i.e., dependent upon stimulation of DA release.<sup>46,47</sup> Methylphenidate and phenmetrazine appear to be similarly effective.

In approximately 60% of patients, amantadine has a clinically significant antiparkinsonian effect which may be enhanced in the presence of levodopa.<sup>48</sup> Since amantadine appears to increase the release of DA and to decrease its reuptake,<sup>47</sup> patients who respond to amantadine (indicating that their DA receptors are still capable of responding to DA) generally respond to treatment with levodopa. Con-

versely, patients who respond poorly to amantadine usually exhibit little if any response to levodopa.<sup>7</sup> Amantadine may provide additional benefit to a levodopa responder and should be considered whenever maximal benefit cannot be achieved with levodopa alone. Amantadine is commonly given as 200 mg daily in two equal doses. Its effectiveness may decline over a period of two or three months, but as with many of the antiparkinsonian agents, a brief respite from therapy may allow prolonged benefit.

In contrast to levodopa and the anticholinergic agents, amantadine is relatively free from serious side effects. When side effects do occur, they are usually mild, transient, and totally reversible.<sup>36,49,50</sup> Perhaps one of the most disturbing side effects of amantadine is that of livedo reticularis which commonly presents as a diffuse, reddish-blue mottling of the skin, commonly in conjunction with a mild pedal edema. It is most often seen in the lower extremities but can also be seen on the arms. The proposed mechanism of this side effect is merely an extension of amantadine's pharmacologic action; increased peripheral release of catecholamines causes a peripheral vasoconstriction, which leads to a cutaneous discoloration.<sup>49</sup> The reported incidence varies from less than 2%<sup>50</sup> to almost 100%,<sup>51</sup> but there is almost universal agreement that this side effect is relatively benign, completely reversible, and usually does not require discontinuation of the amantadine. Other infrequently reported side effects include insomnia, dysarthria, drowsiness, affective changes, and rarely, convulsions.

### *Decreasing Dopamine Reuptake by Pre-Synaptic Sites*

The tricyclic antidepressants are known to inhibit pre-synaptic reuptake of both NE and epinephrine and, although it was theorized that these agents may similarly inhibit pre-synaptic reuptake of DA at the striatum, current evidence indicates that they do not.<sup>11,52,53</sup> These agents do possess some antiparkinsonian effects, but this is most likely due to their mild anticholinergic properties. They may be useful in the treatment of the depression that often accompanies Parkinson's disease. The most commonly used agents include imipramine, desipramine, and amitriptyline.

### *Decreasing Dopamine Catabolism*

The only medications marketed at present with the capability of decreasing DA catabolism are the monoamine oxidase (MAO) inhibitors. These agents should never be used in conjunction with levodopa since, in addition to inhibiting the catabolism of levodopa, they inhibit the catabolism of the levodopa metabolites (DA, NE and epinephrine).<sup>21,54</sup> The resulting accumulation of these potent pressor agents could lead to a hypertensive crisis.

Research is in progress to identify agents that may

block or inhibit the degradation of DA.

## CONCLUSION

Neuropharmacology has done much to delineate the role that each neurotransmitter plays in the CNS. The burden of further advances now rests with the neurophysiologist. An electrophysiologic, anatomic, and neurochemical transmission map of the basal ganglia, similar to that presently available for the spinal motor apparatus and the cerebellum, needs to be developed. When this becomes available, many of the unanswered questions and paradoxical observations of parkinsonism may fall into place.<sup>8</sup>

With a firm understanding of present knowledge of the structure and function of the basal ganglia, clinicians should be able to prescribe rational pharmacotherapy for the parkinsonian patient. Further, the informed clinician can objectively and intelligently evaluate the direction and application of future developments in the pharmacotherapy of Parkinson's disease.

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## **SNF Program Expanding**

Outpatient services, home care, and same day surgery, all covered by Blue Cross, are all ways to receive hospital type services without having to be a patient in the hospital.

Another area that has expanded very rapidly of late at Blue Cross of Maine is coverage for care in a Skilled Nursing Facility (SNF). A SNF does not provide acute care as available in a hospital but is engaged in providing skilled nursing care and related services for patients who require nursing care, or rehabilitation services for the rehabilitation of the injured, disabled or sick.

A pilot project for care in a Skilled Nursing Facility had been available in only three institutions in Maine until recently, when the program was expanded to cover care in twelve facilities. They include: Aroostook Health Center SNF (A.H.C. Hospital), Bodwell House (Regional Memorial Hospital), Community General Hospital SNF (Community General Hospital), Hibbard Nursing Home, Houlton Regional Hospital SNF, Jewish Home For The Aged, Mt. Desert Hospital SNF (Mt. Desert Island Hospital), National Medical Care of Portland, Inc., Orono Nursing Home, Inc., Portland City Hospital SNF, Ross Home-Kelly Five, and the Henry Strater Wing (York Hospital).

Recognizing SNF care as a very effective alternative to inpatient hospitalization, Blue Cross and Blue Shield of Maine provides benefits for two days of SNF care for each unused hospital benefit day on the subscriber's contract. In other words, if a subscriber with a 121 day Blue Cross contract goes in the hospital for 21 days, then is transferred to a SNF, he could have as much as 200 days of skilled care if necessary.

Under this program, admission to a SNF may be a direct transfer from an acute general hospital or a direct admission to the SNF.

The actual benefits of the program are exactly the same as those shown in the Blue Cross contract for care in a hospital, except for the provision of two days of care in a skilled nursing facility for each benefit day provided by the contract. Blue Shield benefits for physicians' services will be provided at the same level that would be provided if the patient were confined in a hospital.

The Skilled Nursing Facility Pilot Program, designed to save health care dollars by placing eligible patients in a less costly skilled care environment, will continue on an experimental program until enough data is available to support a decision to either make it a permanent part of the contract or to limit its availability.

*Reserve these dates . . . June 11-14, 1977*

**124th Annual Session**  
**Maine Medical Association**  
*Treadway-Samoset — Rockport, Maine*

**Monday, June 13**

Presented by Tufts University  
School of Medicine, Boston

**"Expensive Procedures in Diagnostic Medicine"**

1. What do they offer?
2. Who should order them?
3. Who should receive them?
4. Who should pay for them?

9:00 to 9:20 A.M. **"General Background and Policy"**

9:20 to 9:40 A.M. **"CAT Scanning"**

9:40 to 10:00 A.M. **"GI Endoscopy, Esophageal Motility Study, Fiberoptic Endoscopy of the Digestive Tract, Cannulation and Papil-  
lotomy, Laparoscopy"**

10:15 to 10:35 A.M. **"Echocardiography, Cardiac Catheterization, Coronary Arteriography and Exercise Testing"**

10:35 to 10:55 A.M. **"Surgical Procedures With**

**Questionable Indications — Cost, Benefit Considerations"**

10:55 to 11:15 A.M. **"Arthroscopy — Nature of the Procedure, Indications, Use and Complications"**

11:15 to 12:15 P.M. **Panel Discussion**

1:45 to 2:45 P.M. **Plenary Session**

3:00 to 4:00 P.M. **Workshops: Orthopedics, Cardiology, GI & Surgery, Neurology & X-ray**

**Tuesday, June 14**

9:00 to 10:30 A.M. **"Child Abuse/Neglect in the State of Maine"**

10:45 to 12:00 M. **"Screening for Genetic Defects in Maine"**

2:00 to 3:00 P.M. **"Drug Interactions"**

3:00 to 4:00 P.M. **"Modern Drug Usage"**

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**EVENTS OF INTEREST —**

**Saturday, June 11**

2:00 P.M. First Meeting of the House of Delegates

Presentation of the A. H. Robins' Physician Award for Community Service

Presentation of the Maine Blue Cross and Blue Shield "Award of Appreciation"

**Sunday, June 12**

A.M. Reference Committee Meetings

2:00 P.M. Second Meeting of the House of Delegates

Election of President-elect, Executive Committee District Members and AMA Delegate and Alternate

**SUNDAY EVENING — LOBSTER BAKE**  
**MONDAY EVENING — ANNUAL BANQUET**

# News, Notes and Announcements

## Newer Clinical Approaches to Venereal Diseases

**Sponsored By**  
**American Medical Association**  
**Co-Sponsors**  
**The State Medical Societies of**  
**New Hampshire and Vermont**  
**May 19, 1977**

### Wentworth-by-the-Sea, Portsmouth, New Hampshire

There are new diagnostic procedures and new ways of managing sexually transmissible diseases. In fact, now there are even non-typical body locales in which VD is appearing.

You'll learn all this and more at this one-day course presented primarily for physicians in private practice, interns, residents, medical students, public health personnel, and others.

The focus is on the scientific and clinical aspects of venereal diseases with special attention to diagnosis and management. The program features discussions on gonorrhea and non-gonococcal urethritis; primary, secondary, and latent syphilis; chancroid, granuloma inguinale and lymphogranuloma venereum; herpes genitalis; the common vaginitides; genital warts and molluscum contagiosum; pediculosis pubis and scabies.

This course is acceptable for Category I credit (7 hours) toward the AMA Physician's Recognition Award in Continuing Medical Education.

### "New Directions in Breast Cancer Management"

**May 25, 1977**

**Sheraton-Wayfarer Motor Inn, Bedford, New Hampshire**

**Sponsors: Breast Cancer Network Demonstration Project,**  
**Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical**

**Center, Office of Continuing Medical Education, Dartmouth Medical School, New Hampshire Division, Inc., American Cancer Society, Catholic Medical Center.**

**Presentations by: Drs. John Wolfe, Eugene DeSombre, Gianni Bonadonna, Benjamin Byrd, Christopher Gates, Robert Goldwyn and by Susan Hillenbrand, R.N., M.S.**

**Accreditation: Approved for 7 hours of continuing education credit — American Medical Association, and for 7 hours of prescribed credit by the American Academy of Family Physicians.**

**Further Information: Contact Susan B. Baird, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Hanover, N.H. 03755, (603) 643-4000 Ext. 2271.**

### Third Annual Maine Biomedical Symposium

The Third Annual Maine Biomedical Science Symposium will be held at the University of Maine at Orono, May 26-27, 1977. Like its successful predecessor, this symposium will provide a common forum for Maine clinicians, biomedical scientists, and educators to present new advances in their respective fields, to report on research projects, to explain new methods, and to establish greater communication within the biomedical community in Maine.

The topics of the sessions in the 1976 symposium will be as follows:

Behavior (John M. Ringo, Ph.D., UMO)

Human Genetics (Pomeroy Sinnock, Ph.D., Genetics Counseling Center, Ellsworth)

Cancer (Lawrence M. Cutler, M.D., Bangor)

Cardiology (William S. Wilson, M.D., Bangor and Peter W. Rand, M.D., Cape Elizabeth)

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Cell and Molecular Biology (Seth Tyler, Ph.D., UMO)  
Immunology (Larry Mobaratton, Ph.D., Assistant Staff Scientist, Jackson Laboratory, Bar Harbor)  
Virology (Mary Ann Jerkofsky, Ph.D., UMO)

Each session will include a general lecture by a distinguished worker in the field designed to provide an overview of the state of the art in that field.

In addition to regular session presentations, there will be one evening session of poster-presentations on any topic. The informal give and take dialogue characteristic of poster presentations will augment the more formal seminar sessions.

The success of the previous symposia demonstrated the great need and desire for greater communication between scientists and clinicians in Maine. Let us build upon the others by making the third symposium even better.

**Fourth Annual  
Aspen Mushroom Conference  
Hotel Jerome  
Aspen, Colorado  
August 7-12, 1977**

The Fourth Annual Aspen Mushroom Conference is designed for physicians, amateur mycologists and scientists interested in the identification and toxic properties of mushrooms. The Conference is sponsored by the Colorado Mountain College, Glenwood Springs and the Beth Israel Hospital, Denver, Colorado.

An outstanding group of Colorado and visiting mycologists and physicians will serve as faculty for the Conference. Dr. Alexander H. Smith, the senior faculty member, is the author of a *Field Guide to Western Mushrooms* and is Professor of Botany at the University of Michigan. Dr. Harry Thiers, Professor of Botany,

San Francisco State University, author of *California Mushrooms* will conduct a course on advanced toxonomy. Dr. Roy Watling, Principal Scientific Officer, Royal Botanic Garden, Edinburgh, Scotland, author of *British Fungus Flora* will teach a course on mushroom cultivation.

The program will be structured for the beginner as well as the advanced student by offering independent teaching sessions for each group. Didactic sessions and refresher courses on mushroom identification will be held in the early mornings and late afternoons at the novice and advanced student levels. The program will include mushroom microscopy for a limited number of advanced students, and mushroom chemistry and chromatography. Courses on advances in the diagnosis and treatment of mushroom poisoning and on hallucinogenic mushrooms will be offered to physicians and others interested in these subjects.

Generally, in the late summer, the Aspen mountains are productive of a wide variety of mushrooms. Experienced leaders will conduct daily forays into the surrounding mountains to collect edible and poisonous species and study their field characteristics.

Adequate time will be allowed to participate in leisure mountain activities including the renowned Aspen Music Festival.

AMA Physician Recognition Award: Up to 30 hours category II.

For further information contact: Aspen Mushroom Conference, c/o Beth Israel Hospital, 1601 Lowell Boulevard, Denver, Colorado 80204, (303) 825-2190 Ext. 354.

**M.D. Vacancies in  
Project USA**

Project USA, the American Medical Association's program to recruit physicians for short-term service (usually two weeks) has

year round vacancies at Indian Health Service facilities, and National Health Service Corps rural communities. Project USA physicians receive \$500 a week plus round trip air coach fare, and family housing accommodations are provided.

Malpractice insurance coverage is furnished under the Federal Torts Claims Act for service on Indian reservations, however, the physician must provide his/her own malpractice insurance at

a NHSC site. It is a simple procedure to extend an existing coverage to include short-term service at a NHSC location. Any expense involved in this process will be assumed by Project USA.

Physicians interested in participating in this program are requested to contact John Naughton, AMA, 535 N. Dearborn, Chicago, Illinois 60610; (312) 751-6388.

#### TUBAL STERILIZATION: An Update of the Irving Technique — *Continued from Page 133*

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## The Application of Charcoal Hemoperfusion to Paralytic Shellfish Poisoning

PETER W. RAND, M.D., FRANK H. LAWRENCE, M.D., LOUIS A. PIRONE, JR.,  
JEFFREY R. LAVIGNE and ELEANOR LACOMBE\*

Paralytic shellfish poisoning results from the ingestion of clams, mussels, and other molluscs which have concentrated the toxins of marine dinoflagellates of the genus *Gonyaulax*. Saxitoxin, a small (372 MW) nonprotein compound 50 times more lethal than curare, has been isolated from the West coast species *G. cantanella*.<sup>1</sup> At least four structurally similar neurotoxins (including saxitoxin) have been identified in the East coast species *G. tamarensis*.<sup>2,3</sup> Although this latter organism has caused poisoning endemically in the St. Lawrence River estuary and along the Canadian shores of the Bay of Fundy (187 cases with 24 fatalities between 1882 and 1970<sup>4</sup>), it has, until recent years, caused little concern along the Maine coast. Previous evidence for its presence in Maine waters is limited to a long-recognized population of affected shellfish in eastern Washington County, occasional detection of minimal toxicity levels in other areas,<sup>5</sup> and an illness with suspicious symptomatology among employees of mussel processing plants in Brooklin and Southwest Harbor in 1943.<sup>6</sup>

The sudden appearance in September 1972 of intense *Gonyaulax* blooms along the shores of northern Massachusetts,<sup>7</sup> New Hampshire,<sup>8</sup> and southern Maine, and the 28 intoxications which followed, presented a new and urgent public health crisis at that time. As might be predicted from the fact that the dinoflagellate survives winter in an encysted stage, blooms recurred in 1974, 1975, and 1976. Although each State has responded to this problem

by effectively intensifying its monitoring and harvest control program, the protection of unwary visitors from this occasional but lethal hazard will always be difficult because of the remote location of many coastal areas and the patchy nature of *Gonyaulax* blooms.

Paralytic shellfish poisons (PSP) act by blocking sodium channels in nerve and muscle membranes.<sup>9,10</sup> Symptoms typically progress from circumoral to peripheral paresthesias and to paralysis which, terminally, involves the muscles of respiration. The rate of this progression is dose-related, with death occurring as early as two hours.<sup>11</sup> Since no antidote has been found, treatment has been limited to standard methods including emesis induced with ipecac, the administration of activated charcoal, assisted ventilation, and general supportive measures.

In view of the threat to public health represented by the newly established population of *G. tamarensis* in Maine waters, a cooperative liaison between medical and marine groups<sup>†</sup> has been established to assure rapid communication, to provide education, and to investigate more efficient methods of treating paralytic shellfish poisoning. In this paper we report the results of subsequent research which, although intended initially to evaluate only the in vitro effectiveness of emergency peroral treatments, soon progressed to animal experiments which have demonstrated an effective, direct method by which PSP detoxification may be achieved in vivo.

\*Research Department and the Poison Control Center, Maine Medical Center, 22 Bramhall Street, Portland, Maine 04102.

Reprint requests to: Peter W. Rand, M.D., Research Department, Maine Medical Center, 22 Bramhall Street, Portland, Maine 04102.

†The Poison Control Center, Research Department, and Department of Audiovisual Resources of the Maine Medical Center; the Maine Department of Marine Resources, the Maine Department of Health Resources, and the Bigelow Laboratories for Ocean Sciences.

## MATERIALS AND METHODS

The toxins employed in this study were:

- (1) Saxitoxin (STX), kindly supplied as Reference Standard Shellfish Poison, 100 µg/ml by the United States Food and Drug Administration, Cincinnati, Ohio. This material served both as a standard for the mouse PSP bioassay<sup>‡4,12</sup> and also as a reagent in detoxification experiments.
- (2) An extract containing *G. tamarensis* toxins (GTX), 553 µg/100 gm meat, prepared according to standard methods<sup>4</sup> from sea clams (*Spisula solidissima*) generously supplied by John W. Hurst, Department of Marine Resources, West Boothbay Harbor, Maine.

Potential detoxifying agents were:

- (1) 0.1 M sodium hydroxide.
- (2) Charcoal slurry for oral use (Activated Charcoal, USP, Food Grade, J.T. Baker No. 1-1560 1 gm/3 ml 0.5 percent sodium carboxymethylcellulose), issued by the Maine Medical Center Pharmacy.
- (3) Activated charcoal particles for hemoperfusion (Whitcarb Grade 950, 12 x 30 mesh, Witco Chemical Corporation, 277 Park Avenue, New York, NY 10017), washed according to the procedure described by Van Wagenen, et al,<sup>13</sup> who demonstrated the hemodetoxifying superiority of this product over many other forms of charcoal.

## PROCEDURES

Since the effectiveness of activated charcoal as a non-specific adsorbant of ingested toxins is well established, and since alkalization is known to affect the chemical stability of saxitoxin,<sup>14</sup> initial in vitro experiments (Part A) were designed to determine the usefulness of these approaches, both singly and in combination, against paralytic shellfish poisons. Following the dilution steps outlined by Prakash,<sup>4</sup> working solutions of both STX (0.577 µg/ml) and GTX (0.503 µg/ml) were prepared which, after the intraperitoneal injection of 1.0 ml, killed 20 gm mice within 5-7 minutes. Prior to final dilution, the sea clam extract (GTX) was passed through an Amicon type PM 10 ultrafiltration membrane to remove particles larger than 10,000 M.W

### 1. Charcoal Slurry:

To 10 ml aliquots of these working solutions (pH 3-4), increasing amounts of activated charcoal slurry were added. The mixtures were vortexed, allowed to stand for 10 minutes, revortexed, and filtered through Whatman No. 1 filter paper. Residual toxicity of the filtrate was again measured by the mouse bioassay technique.

### 2. Alkalization:

To assess the influence of alkalization alone, sufficient 0.1 M sodium hydroxide was incorporated into the final dilution of working solution to increase

the pH to  $8.0 \pm .2$ . After ten minutes of incubation at room temperature, toxicity was remeasured.

### 3. pH vs. Charcoal:

Finally, to determine if alkalization altered the adsorbency of GTX on activated charcoal, varying amounts of charcoal slurry were added to 10 ml aliquots of alkalized shellfish extract and the results compared with the initial experiments.

After it had been established that activated charcoal reduced the toxicity of PSP in vitro, one of us (JRL) suggested that its effectiveness as a direct hemodetoxifying agent be explored. This proposal was supported by the recent successful application of this method to overdoses with a wide variety of drugs and toxic compounds,<sup>15,16</sup> by the commercial availability of charcoal hemoperfusion cartridges for clinical use, and particularly by the evident need for a reliable, direct, and rapid method to reduce circulating PSP levels in patients presenting with progressive neurological involvement.

For this study (Part B), 13 pairs of Sprague-Dawley rats (Crl: COBS CD (SD) BR, Charles River Breeding Laboratories, Wilmington, Massachusetts) 250-390 gms, matched for sex and weight ( $\pm 3$  gm) were anesthetized with intraperitoneal sodium pentobarbital (5.0 mg/100 gm), heparinized (100 units per 100 gm), and attached via femoral arterial and venous cannulae (PE-50) to an extracorporeal circuit having a total volume of 6.0 ml. The system (See Figure 1) included, in order from the arterial cannulae, a roller pump, a top-perfused drip chamber containing either activated charcoal (1.5 gm, dry weight) or an equal volume of glass beads, and a T-connector for the infusion, by syringe pump, of STX, selected over GTX for this intravenous application because of its relative freedom from extraneous materials. Finally, a syringe was placed in-line to clear air bubbles from the extracorporeal system.

Preliminary runs demonstrated that the animals would remain alive indefinitely (greater than 2 hours) when hemoperfused in the absence of added toxin, and also that the degree of anesthesia used did not alter the response of rats to STX. In subsequent studies, an extracorporeal flow of 3.5 ml/min was established, following which a slow infusion (0.051 ml/min) of STX was started. The concentration of toxin in normal saline used in each pair was adjusted, on a weight basis, to cause respiratory paralysis in unprotected (glass beads) animals in approximately 20 minutes. During this period, an amount of blood equal to 3-4 times each animal's total blood volume traversed the extracorporeal circuit. Both this limited exposure to charcoal and the continuing infusion of toxin increased the significance of any prolongation of death time in the charcoal-hemoperfused animals.

## RESULTS

### Part A — In Vitro Studies:

1. PSP adsorbency of oral charcoal slurry: 8 different volumes of charcoal slurry from 70-160 µl/10

<sup>‡</sup>18-22 gm mice, strain B6DF<sub>1</sub>/J, CF value 0.32, supplied by the Jackson Laboratories, Bar Harbor, Maine.

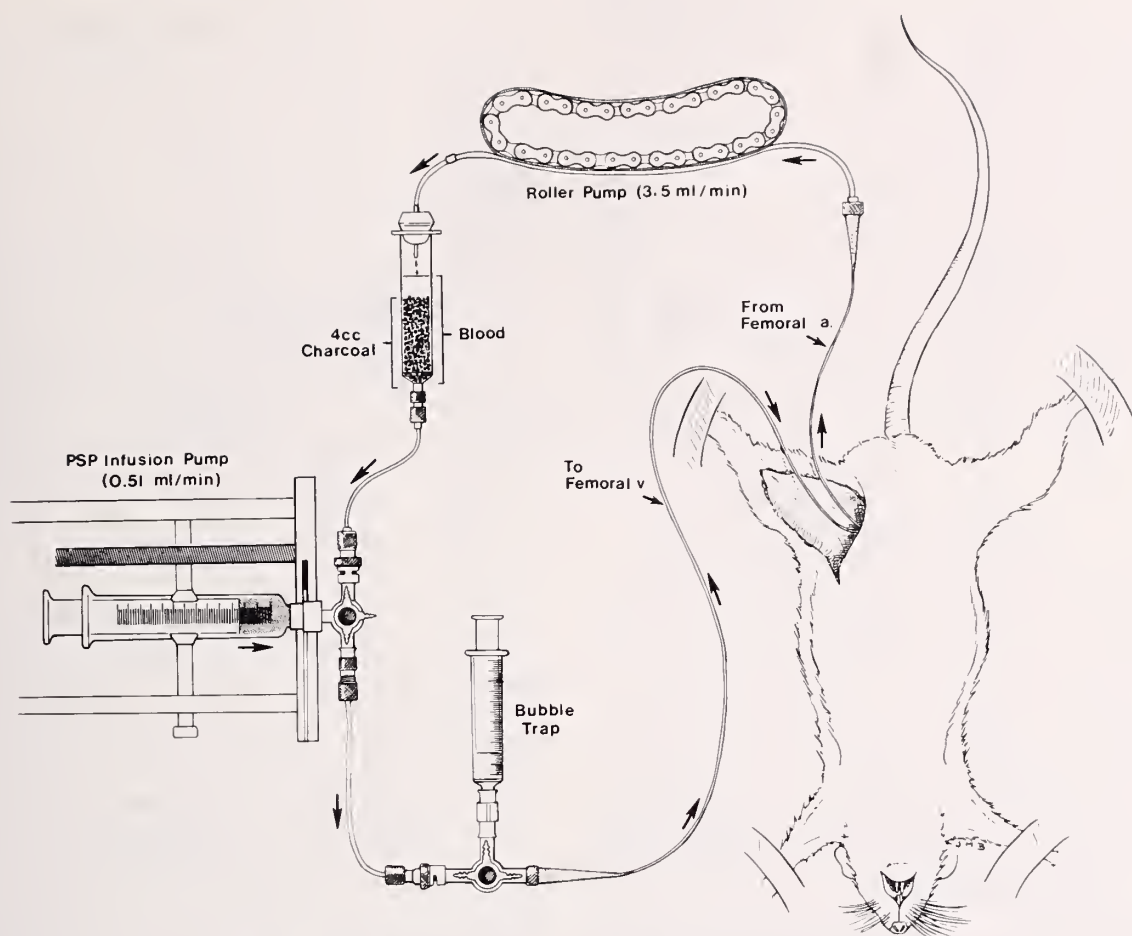


Fig. 1. System for extracorporeal charcoal PSP hemodetoxification.

ml STX were studied (6-9 mice each). A significant extension of control (5-7 min.) death times occurred at the 140  $\mu$ l level. At and above this ratio of charcoal (dry weight) to toxin (8.7 mg/ $\mu$ g), all mice lived. When this experiment was repeated with ultra-filtered GTX, the ratio of 33.2 mg/ $\mu$ g was obtained.

2. Effective Alkalinization: Since the several toxins of *G. tamarensis* respond individually to varying pH<sup>3</sup>, Maine coast shellfish extract, rather than saxitoxin alone, was investigated. After titration with 0.1 NaOH to pH 8.0, average death times were extended from 6'0" to 11'29" (range: 6'53"-25'10", n = 14), not including one animal which survived.

3. Effect of Alkalinization plus Charcoal: Since it is recognized that a shift in pH may greatly reduce the adsorption of ionizable substances on the surface of activated charcoal,<sup>17</sup> we had hoped to use these experiments to detect any difference in the effectiveness of charcoal adsorption at pH 8. We found, however, that approximately the same ratio of charcoal to original (pre-titrated) GTX (30.1 mg/ $\mu$ g) was necessary to achieve universal survival. Charcoal adsorption of GTX is not enhanced at pH 8, rather, its effectiveness against the remaining active toxin is diminished, perhaps by blockage of active sights by alkaline-deactivated molecules.

Part B — Hemoperfusion Experiments:

Of 13 pairs of rats studied, 11 demonstrated distinct delay of their inevitable respiratory arrest (See Figure 2). The two inconsistent results occurred within the first five experiments in which very fine (femoral cannulae were used and no drip chamber was provided to monitor flow continuously. We suspect obstruction of the arterial cannula prevented blood-charcoal contact in these two animals. Despite inclusion of this contrary data in the final tabulations, the differences between control and charcoal-hemoperfused animals with respect to both death time and total toxin received is of high statistical significance ( $P < 0.01$ ).

Sufficient purified extract was not available for a parallel series of rat hemoperfusions with GTX. The efficiency of activated hemoperfusion charcoal to adsorb these toxins was demonstrated, however, in a series of experiments in which mice were injected intraperitoneally with either 1 ml GTX extract (0.503  $\mu$ g/ml), which caused respiratory arrest within 5-7 minutes (6'22", SD 18", n = 11), or with the supernatant of the same material previously mixed with hemoperfusion charcoal. At a rate of 318 mg charcoal to 1  $\mu$ g GTX, all mice (n = 11) survived. This concentration of charcoal was approximately double that necessary, in a parallel study, to detoxify STX (173 mg/ $\mu$ g). Adsorbence of extraneous

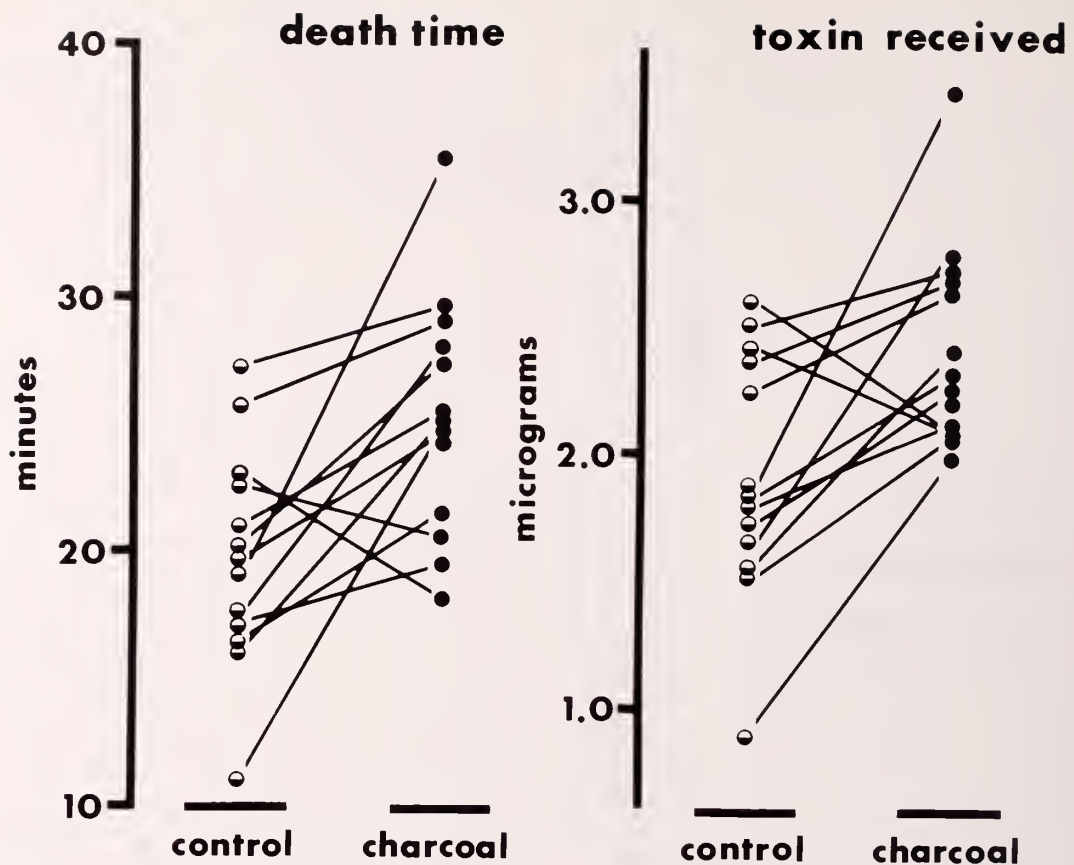


Fig. 2. Individual death times and toxin doses for glass bead (semi-closed circles) and charcoal (closed circles) hemoperfused rats.

material in the relatively less pure GTX extract may explain this difference.

Finally, to demonstrate that activated charcoal hemoperfusion reverses as well as delays PSP intoxication, a single study was performed in which respiratory excursions and arterial blood pressure levels were recorded in glass-bead and carbon-hemoperfused rats receiving a 20 minute infusion of STX sufficiently concentrated to cause death in the glass bead animal within a minute of the end of the infusion. Following a period of respiratory instability during the last seven minutes of toxin infusion, the charcoal hemoperfused animal recovered within two minutes and remained healthy to the end of the experiment 22 minutes later.

In summary, these experiments demonstrate that both STX and GTX are adsorbed on activated charcoal slurry for oral administration use, that alkalization at room temperature definitely but variably reduced the potency of these toxins, that alkalization does not enhance charcoal adsorption, that activated charcoal is effective in removing PSP in an extracorporeal system, and that survival from an otherwise lethal dose may be achieved by this method.

#### DISCUSSION

Paralytic shellfish poisoning is no longer simply an academic problem on the northern New England

coast. *G. tamarensis* is consumed by all varieties of indigenous clams, mussels, and quahogs<sup>4</sup> and its toxins may be doubly concentrated by carnivorous gastropods (whelks, moon snails, dog whelks) which prey on these molluscs.\* Indeed, one severe and one moderate human intoxication followed a family meal of moon snails (*Polinices*) in 1975.<sup>18,19</sup>

In addition to the intensified surveillance and harvest control programs which have been instituted by marine fisheries authorities in each State to prevent PSP intoxication, it is imperative that the medical profession be aware of the threat, recognize its symptoms, understand its cause, and be ready to apply the most effective treatment available. Physicians should know where to ask for help\*\* or, subsequently, to forward the selected epidemiologic data† which are essential for more specific understanding of this local disease.

Once adsorbed from the gastrointestinal tract, PSP acts by obstructing the influx of sodium<sup>20</sup> through the membranes of peripheral nerves and muscles. It does not cross the blood-brain barrier;<sup>21</sup>

\*It should be emphasized that lobsters, crabs, and finfish are never affected.

\*\*Poison Control Center, Maine Medical Center, 22 Bramhall Street, Portland, Maine 04102. Tel: (207) 871-2381.

†John W. Hurst, Department of Marine Resources, Fisheries Research Station, West Boothbay Harbor, Maine 04575. Tel: (207) 633-5572, and Poison Control Center, as above.

therefore, its respiratory and circulatory effects cannot be modified with central nervous system stimulants. Hypotension, which results from direct relaxation of arterial smooth muscle as well as from interruption of vasoconstrictor nerve impulses, is occasionally seen, but more frequently is compensated for by catecholamine release.<sup>22</sup> Drugs designed to enhance transmission at the myoneural junction have little value and, since the heart is not directly affected, digitalis preparations are not useful.<sup>23</sup> It has been shown,<sup>24</sup> however, that the toxin is excreted by the kidneys and diuretic therapy has been suggested.<sup>4,23</sup> Indeed, considering the potency and site-specificity of modern agents, their aggressive use in combination with fluid replacement may prove to be an effective emergency treatment for PSP intoxication which could be instituted at the scene. We are currently evaluating the effectiveness of this approach in laboratory animals.

By whatever method, lacking a specific antidote to counteract the toxin at its site of action, the therapeutic goal must be to minimize its concentration in the blood stream as rapidly as possible. At the first signs of intoxication, further gastric absorption may be halted by evacuation of the stomach. From the present study, subsequent alkalization (with sodium bicarbonate) and installation of charcoal slurry appear to be indicated to detoxify and adsorb any residual poison.

In advanced cases, attention must be focused on lowering blood toxin levels. From our observations, activated charcoal hemoperfusion may provide a direct method of achieving this end. In recent years an extensive literature has appeared describing the effectiveness of activated charcoal hemoperfusion in reversing a wide variety of toxins, both in experimental animals<sup>15,16,25-27</sup> and patients,<sup>28-30</sup> and at least two manufacturers<sup>‡</sup> have introduced extracorporeal charcoal units for clinical use. The opinion has been expressed that "In contrast to hemodialysis, charcoal hemoperfusion is simple to initiate, less expensive in terms of manpower and equipment, and gives superior clearance data. . . ."<sup>29</sup> The technique, however, does require personnel experienced in vascular cannulation, heparinization, and other aspects of extracorporeal perfusion, as well as laboratory facilities capable of rapid and frequent measurements, particularly of platelet count, blood glucose, and serum calcium levels, each of which may be specifically depressed by exposure of blood to charcoal.<sup>25,31</sup> Since it has been briefly mentioned in earlier papers<sup>32,33</sup> (and confirmed in our own preliminary experiments) that saxitoxin passes through semipermeable membranes, hemodialysis also warrants evaluation as a PSP detoxifying procedure. Continued extracorporeal perfusion experiments to compare its

efficiency with that of the charcoal system are scheduled.

Despite the demonstration of a direct approach to the treatment of paralytic shellfish poisoning, further research is needed in three areas before effective management of this problem can be obtained. First, much more must be known about the environmental requirements of *G. tamarensis* before it will be possible to predict its blooms; second, ongoing sophisticated neuropharmacologic research must be given the support necessary to develop an effective antidote; and, finally, but of major importance to future research into the monitoring, clinical diagnosis, and treatment of paralytic shellfish poisoning, a sensitive analysis must be devised by which the toxin may be quantitated in blood, urine, and tissues.

#### ACKNOWLEDGEMENTS

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# Twice Daily Treatment of Pneumonia With Cephadrine

D. L. CALOZA, JR., M.D.\* and GERALD E. BERNFELD\*\*

## ABSTRACT

The clinical efficacy and safety of twice (b.i.d.) and four times (q.i.d.) daily regimens of cephadrine capsules (2 gm per day for approximately nine days) were compared in a multicenter study of 180 patients with lobar pneumonia or bronchopneumonia due to *Streptococcus pneumoniae*. Although there were some differences in results, none were of statistical significance, and the regimens appeared to be equally safe and effective.

## INTRODUCTION

Bacterial pneumonia continues to be an important and intriguing clinical problem. Approximately two million cases occur in the United States each year, accounting for 10 percent of hospital admissions and ranking pneumonia fifth among the leading causes of death. The symptoms and signs of acute pneumonia are quite dramatic, and the ease of radiographic confirmation so readily available, that the clinician usually encounters little difficulty in recognizing a patient with pneumonia. The difficulty lies in determining which agent among many potential pathogens is the actual cause, since the proper selection of an antimicrobial drug and the early resolution of infection depend on the accuracy of the clinician's diagnostic suspicions.<sup>1</sup>

Cephadrine,<sup>†</sup> a new semisynthetic cephalosporin, has been shown to have a broad spectrum of antimicrobial activity *in vitro* and *in vivo* against most gram-positive organisms, including penicillin-resistant staphylococci, and most gram-negative organisms responsible for respiratory tract and urinary tract infections as well as infections of the skin and soft tissues.<sup>2</sup> It is acid stable, readily absorbed from the gastrointestinal tract, and excreted essentially unchanged in the urine.<sup>2,3</sup> Clinical trials involving nearly 6,000 patients with various infectious diseases have demonstrated the efficacy and safety of cephadrine capsules or oral suspension when given four times daily (q.i.d.). Satisfactory (excellent or good) responses were observed in 89.6 percent of the patients with infections of the respiratory tract.

In 1944, Tillett, et al reported successful results in

the treatment of patients with pneumococcal pneumonia when penicillin was administered on a schedule that omitted doses for periods of 12 to 16 hours at night.<sup>4</sup> Tompsett, et al, who conducted an investigation of the effectiveness of "discontinuous" or "continuous" penicillin therapy in a group of patients with pneumococcal pneumonia, found that an initial "discontinuous" regimen of one or two daily doses of sodium penicillin G adequately substituted for the use of a single injection of penicillin in oil that provided a continuous concentration of the antibiotic in blood.<sup>5</sup> Eagle and colleagues confirmed that a number of bacteria susceptible to penicillin remain dormant for various lengths of time after direct bactericidal action ceases. Bacteria do not resume multiplication for several hours after penicillin concentrations fall below effective levels, at which time host defenses continue to dispose of damaged organisms.<sup>6-11</sup> Ampicillin and the tetracyclines also have been shown to be effective when administered twice daily.<sup>12,13</sup>

A twice daily dosage regimen offers the advantages of better patient compliance by being more convenient for the patient's daily routine, e.g., the scheduling of doses to avoid meals is eliminated. Noncompliance is particularly common among patients receiving antibiotic therapy and this often results in an exacerbation of the illness being treated, with the added possibility of the development of organisms resistant to the drug. It has been noted that the solution to the problem of noncompliance includes drug regimens that enable fewer and larger doses to be taken.<sup>14</sup> With fewer doses, however, effective concentrations of antibiotics certainly must be attained with each dose.

In studies conducted at The Squibb Institute for Medical Research, average peak serum concentrations of 16.5 micrograms ( $\mu$ g) per ml and peak urine concentrations of 3,200  $\mu$ g per ml were obtained after oral administration of 500 mg cephadrine capsules in fasted subjects, with measurable concentrations still present six hours after administration. Average peak serum concentrations of 24.2  $\mu$ g per ml and peak urine concentrations of 4,000  $\mu$ g per ml were achieved after a 1 gm dose, with over 90 percent of the orally administered cephadrine excreted (in virtually unchanged form) in the urine within six hours.

In view of the available laboratory and clinical evidence supporting the concept of "intermittent" antibiotic therapy for patients with susceptible infections, a clinical study was initiated to evaluate

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TABLE 1

COMPARISON OF TREATMENT GROUPS IN EFFICACY EVALUATION				
Treatment Group	BID - 83 Patients		QID - 80 Patients	
Sex	Male	Female	Male	Female
Number of Patients	49	34	42	38
Age (yrs.)				
Range	7-85	6-69	5-94	11-61
Average	36.6	34.2	32.6	34.0
Duration of Therapy (days)				
Range	5-14		5-14	
Average	9.1		9.1	
Total Dose (gm)				
Range	10-28		10-28	
Average	18.4		18.4	

initiation of treatment and, if possible, additional cultures were made on the fourth day of therapy. Cultures also were repeated on the seventh day and weekly thereafter as long as the therapy continued, and 48 to 72 hours after therapy had ceased. Roentgenograms of the chest were obtained before and after therapy.

The dose of cephradine for all patients was 2 gm per day; either 1 gm b.i.d. or 0.5 gm q.i.d. Patients were randomly assigned to one of the two treatment groups, and the study was conducted under double-blind conditions. Patients in the b.i.d. group received 1000 mg of cephradine (as two 500 mg capsules) as the first and fourth doses each day and identical placebo (two capsules) as the second and

TABLE 2

CLINICAL RESPONSE CORRELATED WITH DIAGNOSIS AND TREATMENT GROUP						
Diagnosis	Treatment Group	Excellent	Overall Response			TOTALS
			Good	Fair	Poor	
Lobar pneumonia*	b.i.d.	40	13†	4	1	58
	q.i.d.	43	10	2	0	55
"Classical" lobar pneumonia**	b.i.d.	1	1	1	0	3
	q.i.d.	1	1	0	0	2
Bronchopneumonia	b.i.d.	11	9	2	0	22
	q.i.d.	17	6	0	0	23
TOTALS	b.i.d.	52	23	7	1	83
	q.i.d.	61	17	2	0	80

\*Confirmed by presence of *S. pneumoniae* in sputum culture.

\*\*Confirmed by presence of *S. pneumoniae* in sputum smear but not in culture.

†Includes one patient with both lobar pneumonia and bronchopneumonia.

the efficacy of cephradine when administered orally twice daily (b.i.d.) in comparison to its efficacy when administered according to the standard q.i.d. dosage schedule.

### PATIENTS AND METHODS

This multicenter study of 180 patients included both adults and children. It did not include any pregnant women or individuals with a definite history of hypersensitivity reactions to penicillins or cephalosporins. Only patients with lobar pneumonia or bronchopneumonia as verified by clinical findings, roentgenogram of the chest, laboratory tests, and microbiologic examinations were admitted to the study. Patients whose sputum cultures did not grow pneumococci were admitted if the diagnosis was verified by the clinical, laboratory, and roentgenographic findings characteristic of "classical" lobar pneumonia.

A sputum specimen was taken less than 48 hours before the first dose of medication for bacterial culture to identify the infecting organism. However, medication was permitted before the results of the cultures were available. The isolated organism was tested for sensitivity to cephalosporins by the Kirby-Bauer method, using discs containing 30 µg of cephalothin. Follow-up cultures and sensitivity testing were repeated approximately 48 hours after

third doses of the day; patients in the q.i.d. group received one placebo capsule and one 500 mg cephradine capsule q.i.d. Treatment was continued for a minimum of 48 to 72 hours beyond the time that the patient became asymptomatic or evidence of bacterial eradication had been obtained.

The eight investigators who participated in this study were provided with guidelines to standardize the evaluation of therapeutic response. The response was designated as either excellent, good, fair, or poor, depending upon the time required for (a) initial improvement, (b) complete clinical resolution, and (c) eradication of the infecting organism.

### RESULTS

The total population of the study consisted of 180 patients: 90 received cephradine twice daily (b.i.d.) and 90 were treated four times per day (q.i.d.). Seventeen patients were excluded from the efficacy evaluation: seven in the b.i.d. group and ten in the q.i.d. group. Most of these patients were excluded because they did not satisfy the microbiologic criteria (i.e., absence of a pathogenic organism, no sensitivity test, inappropriate culture specimen, etc.).

The 163 patients who satisfied the criteria for inclusion in the efficacy evaluation (83 in the b.i.d. group and 80 in the q.i.d. group) are compared in

TABLE 3

ERADICATION OF STREPTOCOCCUS PNEUMONIAE CORRELATED WITH DIAGNOSIS AND TREATMENT GROUP								
Diagnosis	Treatment Group	Eradication Time (days)				Relapse	Not Eradicated	TOTALS
		≤2	3-4	5-6	>6			
Lobar pneumonia	b.i.d.	2	26*	15	13	0	2	58
	q.i.d.	2	21	19	12	1	1	55
Bronchopneumonia	b.i.d.	0	2	4	15	1	0	22
	q.i.d.	1	7	1	12	0	2	23
TOTALS	b.i.d.	2	28	19	28	1	2	80**
	q.i.d.	3	28	20	24	1	2	78†

\*Includes one patient with both lobar pneumonia and bronchopneumonia.

\*\*Does not include three patients with "classical" lobar pneumonia.

†Does not include two patients with "classical" lobar pneumonia.

Table 1 with respect to sex, age, duration of treatment, and total doses of cephadrine received.

*Clinical responses* are correlated with treatment regimen and diagnosis in Table 2. Satisfactory (excellent or good) responses were seen in 90.4 percent of the patients treated with the b.i.d. regimen and in 97.5 percent of the patients in the q.i.d. group. Only one patient (in the b.i.d. group) did not respond to treatment.

*Bacteriologic results* are presented in Table 3 for the 158 patients whose cultures contained *Streptococcus pneumoniae*. The infecting organism was eradicated in 96.3 percent of the patients in the b.i.d. group and in 96.2 percent of those treated with the q.i.d. regimen. Eradication occurred within six days in 61.3 percent of the b.i.d. group and in 65.4 percent of the q.i.d. group. Relapses were noted in one patient in each group, and two patients in each group did not achieve complete eradication of *S. pneumoniae* within the period of the study.

*Safety Evaluation* — All patients enrolled in the study were considered in an analysis of the incidence of adverse reactions and abnormal clinical laboratory findings during and after therapy with cephadrine. Adverse reactions were experienced by 14 of the 180 patients. The incidence of side effects was higher in the q.i.d. group (11.1 percent) than in the b.i.d. group (4.4 percent), and more patients (five) treated with the q.i.d. regimen had multiple adverse reactions than did those who received the b.i.d. regimen (one). Most of the side effects involved the gastrointestinal tract (see Table 4).

Other untoward effects were cutaneous rashes (two patients in the q.i.d. group), vaginitis in one woman treated with the q.i.d. regimen, one instance of drug fever in the b.i.d. group (therapy was discontinued), and dizziness reported by a patient in the q.i.d. group. Therapy was discontinued due to adverse reactions in two patients treated with the q.i.d. regimen, one because of a rash that persisted for two days and the other because of persistent gastrointestinal discomfort (nausea, abdominal pain, and two episodes of vomiting).

Drug-related abnormalities were detected in the white blood cell counts (complete and differential)

TABLE 4

INCIDENCE OF GASTROINTESTINAL SIDE EFFECTS IN PATIENTS TREATED WITH CEPHRADINE			
Side Effect	Treatment Group		TOTALS
	b.i.d.	q.i.d.	
Abdominal pain	2	4	6
Nausea	0	4	4
Diarrhea	1	2	3
Vomiting	1	1	2
Gastric hyperacidity	0	1	1
TOTALS	4*	12**	16

\*These reactions occurred singly in four patients.

\*\*These reactions occurred in six patients; singly in two and combined with at least one other reaction in four patients.

of three patients in the b.i.d. group and two in the q.i.d. group. These irregularities (leukocytosis, leukopenia, lymphocytosis, lymphocytopenia, monocytosis, neutropenia, neutrophilia, and eosinophilia) were mild and transient in each instance.

## DISCUSSION AND CONCLUSIONS

The clinical efficacy and safety of two antibiotic dosage regimens (b.i.d. and q.i.d.) were compared in 180 patients with lobar pneumonia or bronchopneumonia. The daily dose was 2 gm of cephadrine, given either as 500 mg q.i.d. or 1 gm b.i.d. The duration of therapy was comparable (the average duration was 9.1 days for each regimen).

Although the percentage of satisfactory clinical responses was slightly higher among patients treated with the q.i.d. regimen, the bacterial eradication rates were nearly identical in each treatment group, and there were no statistically significant differences between the two groups.

The high percentage of satisfactory responses (90.4 percent) and the high bacterial eradication rate (96.3 percent) in the b.i.d. group further confirm the efficacy of "discontinuous" regimens of antibiotic therapy for patients with pneumococcal pneumonia.

Only 14 of the 180 patients experienced side effects. It is interesting to note that the incidence of side effects was lower in the b.i.d. group but, again,

the difference between the two groups was not statistically significant.

It therefore can be concluded that cephadrine is safe and effective for the treatment of lobar pneumonia and bronchopneumonia due to *Streptococcus pneumoniae* when administered orally according to either a b.i.d. or q.i.d. schedule.

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#### THE APPLICATION OF CHARCOAL HEMOPERFUSION TO PARALYTIC SHELLFISH POISONING Continued from Page 151

## Antimicrobial Spectrum, Pharmacology, and Therapeutic Use of Antibiotics

### III. Cephalosporins

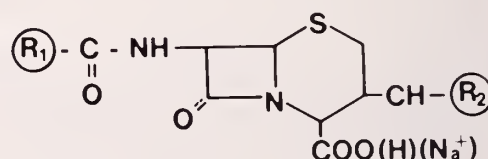
MICHAEL BARZA, M.D. and PETER V. W. MIAO, M.D.

#### INTRODUCTION

The cephalosporins, which are derived from the fungus, *Cephalosporium*, are closely related to the semisynthetic penicillins in structure, mechanism of action, antibacterial spectrum, pharmacological behavior and allergenicity. In the cephalosporins, the beta-lactam moiety is adjacent to a six-membered ring, whereas in the penicillins, it is adjacent to a five-membered ring. This difference appears to enhance the resistance of the cephalosporins to penicillinase. Two investigational drugs, cefamandole and cefoxitin, possess antibacterial spectrums which differ importantly from those of available congeners (Figure 1). (Strictly speaking, cefoxitin is not a cephalosporin but a cephamycin.) Several excellent reviews of various aspects of the cephalosporins have been published recently,<sup>1-3</sup> and the interested reader is referred to these sources for details not covered in this review.

#### MODE OF ACTION AND MECHANISMS OF BACTERIAL RESISTANCE

Cephalosporins, like penicillins, are "bactericidal" antibiotics which act by inhibiting the enzymatic reaction(s) necessary for the production of a stable bacterial cell wall. Recent work suggests that the sites of action of the two groups of antibiotics may not be identical.<sup>4-7</sup> The mechanisms of resistance to cephalosporins and penicillins are similar, except that the cephalosporins are less readily inactivated by beta-lactamase enzymes of many Gram-negative bacteria than are the penicillins.<sup>1,8</sup> The extended spectrums of cefamandole and cefoxitin correlate fairly well with their augmented resistance to beta-lactamase;<sup>1,9</sup> however, other factors, such as permeability barriers to the passage of antibiotic, also play a role.<sup>10-12</sup> Cephaloridine, cephalirin, and cefazolin are more susceptible to inactivation by



R <sub>1</sub>	Generic Name	R <sub>2</sub>
	CEPHALORIDINE	
	CEPHALOTHIN	
	CEFOXITIN*	
	CEPHACETRILE	
	CEPHAPIRIN	
	CEPHALEXIN	- H
	CEPHALOGLYCIN	
	CEPHRADINE	- H
	CEFAZOLIN	
	CEPHANONE	
	CEFAMANDOLE	

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Fig. 1. Structural formulas for the cephalosporins.

staphylococcal penicillinase *in vitro* than is cephalothin,<sup>13,14</sup> but no clinical consequences of this

TABLE 1

## ANTIBACTERIAL ACTIVITY OF THE CEPHALOSPORINS

Species	Susceptibility to Cephalosporins <sup>a</sup>	Differences among Cephalosporins
GRAM-POSITIVE COCCI		
Staph. aureus Staph epidermidis Streptococci Pneumococci	Highly sensitive	Cephalexin, cephradine and cefoxitin one-tenth as active as cephalothin, cefazolin, cefamandole <sup>1,16,17</sup>
Enterococci	Most strains resistant	No important differences
GRAM-NEGATIVE COCCI		
Meningococci Gonococci	Moderately sensitive <sup>18,21</sup>	Not well studied (see text)
GRAM-POSITIVE RODS		
Listeria	Susceptible to cephalothin <sup>22,23</sup>	Not susceptible to cefoxitin <sup>22</sup>
GRAM-NEGATIVE RODS (aerobic)		
H. influenzae	Most strains (80%) moderately sensitive <sup>1,17,19,24</sup>	Cefamandole by far the most active; cephalexin and cephradine very weakly active <sup>24</sup>
E. coli	Moderately sensitive (90%)	Cefamandole, cefoxitin and cefazolin most active <sup>1,9,19,22,25</sup>
Klebsiella	Moderately sensitive (80%)	Cefamandole, cefoxitin and cefazolin most active <sup>1,9,19,22,25</sup>
Enterobacter	Most strains resistant except to cefamandole	Cefamandole most active <sup>1,9,12,19,22,25</sup>
Proteus mirabilis	Most strains weakly to moderately sensitive <sup>1,19,22,25</sup>	
Other proteus (vulgaris, morganii, rettgeri)	Most strains resistant	Cefamandole and cefoxitin markedly more active than others <sup>1,22,25</sup>
Pseudomonas aeruginosa	Resistant	
Serratia	Resistant except 25-50% moderately sensitive to cefoxitin <sup>1,17,22</sup>	Only cefoxitin likely to be active
Salmonella	Most strains (90%) moderately sensitive <sup>1,25</sup>	
Shigella	Most strains moderately sensitive <sup>1</sup>	
ANAEROBIC BACTERIA		
Bacteroides fragilis	Weakly susceptible (50% inhibited) except to cefoxitin	Most strains moderately to highly susceptible to cefoxitin <sup>1,22,25,27</sup>
Other anaerobes including clostridia	Moderately susceptible <sup>25,26</sup>	Cephalexin least active <sup>26</sup>

<sup>a</sup>The terms highly, moderately, and weakly sensitive are used to indicate that the organisms are inhibited by low (usually less than 2 µg/ml), intermediate, or relatively high (e.g., 10-20 µg/ml) concentrations of the cephalosporin.

phenomenon have been demonstrated.<sup>15</sup> Bacteria rarely become resistant to the cephalosporins *in vivo* unless another strain of the organism or bacteriophage intrudes, as may occur in superficial infections such as burns or wounds.

## ANTIBACTERIAL ACTIVITY

Table 1 shows the antibacterial spectrum of the cephalosporins along with important differences among the congeners. In general, these compounds are highly inhibitory to Gram-positive cocci except for enterococci and methicillin-resistant staphylococci; indeed, they are as active as oxacillin and nafcillin against *Staph. aureus* and *Staph. epidermidis*, though less effective than penicillin G against penicillin-susceptible strains.<sup>16</sup> Pneumococci and *Strep. pyogenes* are not as exquisitely sensitive to cephalosporins as to penicillin G or ampicillin, but are still inhibited at concentrations

below 2 µg/ml.<sup>19</sup> Cephalexin, cefoxitin, and cephradine are only one-tenth as active as other cephalosporins against Gram-positive cocci.<sup>1,16,17</sup>

Meningococci are highly susceptible to cephalosporins,<sup>18</sup> and gonococci are moderately susceptible *in vitro*.<sup>20,21</sup> Based on a few isolates, *Listeria* appear to be inhibited by cephalothin but not cefoxitin.<sup>22</sup>

Among common Gram-negative enteric bacilli, only *E. coli*, *Klebsiella*, *Proteus mirabilis*, *Salmonella*, and *Shigella* are regularly susceptible to cephalosporins; however, the two investigational drugs, cefamandole and cefoxitin, have extended the Gram-negative spectrum to include *Enterobacter*, "other proteus," and even some strains of *Serratia*. In addition, *H. influenzae* are highly susceptible to cefamandole.

Cefoxitin exhibits activity against *Bacteroides fragilis* which is unique among penicillins and

cephalosporins; however, its prowess against other anaerobes is not exceptional.

Despite rare instances of antagonism *in vitro*,<sup>28</sup> the cephalosporins have been used in combination with penicillins (carbenicillin) or aminoglycosides with no evidence of interference; indeed, there is some suggestion of synergism with the aminoglycosides *in vivo*.<sup>29</sup> In contrast to the penicillins, including oxacillin<sup>30</sup> and nafcillin,<sup>31</sup> the cephalosporins are not reliably synergistic with aminoglycosides against enterococci.

### CLINICAL PHARMACOLOGY

Pharmacological characteristics of the cephalosporins are summarized in Tables 2 and 3. Only cephalixin and cephadrine are well absorbed by mouth.<sup>37</sup> The presence of food in the stomach delays, and reduces by about one-third, the peak serum level of cephalixin.<sup>3,32</sup> Cefazolin and cephaloridine are well-tolerated intramuscularly.<sup>2</sup> All congeners, except cephalixin, are available as intravenous preparations.

Serum levels of cephalosporins are inversely related to the volume of distribution and the rate of elimination (metabolism and excretion) of the antibiotic. Considerable intra-subject variations are encountered in the serum levels recorded after a given dosage. Typical peak concentrations are shown in Table 2. Cefazolin produces higher serum levels than do other cephalosporins,<sup>33</sup> presumably on account of its smaller volume of distribution and longer half-life (slower elimination). Circulating cephalosporins are reversibly bound to serum albumin, cefazolin being the most highly bound (74-86%). Because protein-bound antibiotic is not antibacterially active nor readily available for diffusion to the periphery, it is useful to compare the peak serum levels of various cephalosporins in terms of free drug. When this is done, the differences among the various congeners are less striking (Table 2).

Cephalosporins, like penicillins, are relatively lipid-insoluble and do not penetrate cells (including polymorphonuclear leukocytes), ocular humors, or prostatic tissue well. However, they readily traverse interstitial<sup>32,70,71</sup> and synovial fluid<sup>72</sup> and limited data suggest fairly extensive passage across the placenta.<sup>73-75</sup> Penetration of cancellous bone is poor.<sup>76</sup> A major drawback to the use of cephalosporins is the low concentration achieved in spinal fluid (Table 2); this deficit appears to explain, at least in part, the disappointing results obtained with these agents in the therapy of meningitis.<sup>18,77,78</sup> There is no evidence that the newer congeners offer an advantage in this respect.

The cephalosporins are actively secreted into bile<sup>79</sup> though this does not constitute a major route of their excretion. Cefazolin is more readily excreted than other congeners into the common-duct bile.<sup>79-83</sup> For example, the following mean concentrations have been reported in choledochal bile

after 1-gram parenteral dosages: cefazolin 31, cephalothin 4, and cephaloridine 9  $\mu\text{g/ml}$ .<sup>80</sup> Cefazolin has been detected in concentrations as high as 50  $\mu\text{g}$  per gram of gallbladder tissue following the administration of 500 mg intramuscularly. None of the cephalosporins passes readily into the common duct in the presence of choledochal obstruction or gallbladder bile in the presence of cystic duct obstruction.<sup>80,82,83</sup>

Elimination of the cephalosporins occurs mainly (50-100%) through the kidneys by a combination of glomerular filtration and active tubular secretion; active secretion of cephaloridine is negligible.<sup>68,84</sup> The transport pump is shared with the penicillins, probenecid, and paraminohippuric acid;<sup>67</sup> all of these compete with the cephalosporins, resulting in a reduced rate of elimination and higher serum levels of antibiotic.<sup>68,84</sup> In addition, cephalothin and cephapirin undergo substantial (30-40%) biotransformation to products which are as much as three-fold less active against Gram-positive cocci, and 8-16 fold less inhibitory to Gram-negative bacilli, than the parent compounds.<sup>56</sup>

The mechanisms of renal excretion and biotransformation of the cephalosporins are so efficient that the serum half-lives of these drugs are short (Table 3); consequently, they must be administered frequently (e.g., every 2-4 hours) for effective therapy of serious infections. Cefazolin and cephaloridine exhibit a longer half-life on account of their slower excretion and minimal degradation; they may be administered less frequently.\*

On the basis of limited data, it appears that the half-lives of the cephalosporins are only minimally altered by mild degrees of renal impairment but may be substantially prolonged by moderate or severe renal disease (Table 3). Precise half-life values (and appropriate drug dosages) for a given degree of impairment are difficult to predict because of inter-individual variations in the rates of nonrenal elimination, and because of the accumulation of bioactive derivatives in the case of cephalothin and cephapirin. Thus, the dosage modifications provided in Table 3 for various degrees of renal impairment are necessarily somewhat arbitrary. For situations in which the half-life of the drug becomes relatively long (e.g., three hours or more), we have adopted the principle of administering a somewhat larger initial dose ("loading dose," eg, 2 g cephalothin or cephapirin, 1 g cefazolin) followed by a "half-dose" every half-life. Cephaloridine should be avoided in patients with renal impairment since it

\*Immediately after parenteral administration, there is a rapid decline in the serum levels of antibiotic due to the combination of distribution and elimination (alpha phase); thereafter, there is a slower decline attributable solely to elimination (beta phase). Strictly speaking, the beta phase provides a more accurate measurement of the biologic half-life; however, most of the half-life values in Table 3 apply to the alpha phase since this may be more clinically relevant with agents which are administered at such frequent intervals as are the cephalosporins.

TABLE 2

COMPARATIVE PHARMACOKINETICS OF CEPHALOSPORINS (Part I)<sup>a</sup>

Agent	500 mg orally (fasting)			Peak serum levels ( $\mu\text{g/ml}$ )			1 g intravenously		Serum protein binding (%)	Penetration (percentage of peak serum level)	
	Total	Free	Total	1 g intramuscularly	Free	Total	Free	Free		CSF normal	CSF inflamed
ORALLY-ABSORBED											
Cephalexin	18 ( <sup>2,32</sup> )	16	—	—	—	80 <sup>b</sup> ( <sup>33</sup> )	70	12 ( <sup>2,33,34</sup> )	Not detectable <sup>c</sup> ( <sup>35</sup> )	1.7 ( <sup>36</sup> )	—
Cephadrine	18 ( <sup>2,37</sup> )	15.5	10 ( <sup>37</sup> )	8.6	See below	8-20 ( <sup>2,37,38</sup> )	—	—	—	—	—
PARENTERAL											
Cephalthin	—	—	—	—	—	—	—	—	—	—	—
Cephapirin	15-24 ( <sup>2,46</sup> )	5.3-7.4	40-60 ( <sup>33,39,43</sup> )	14-21	65 ( <sup>2,33,34,39</sup> )	44-54 ( <sup>2,36,47,48</sup> )	—	—	—	—	—
Cefazolin	64 ( <sup>2,3,42</sup> )	12.8	188 ( <sup>42</sup> )	38	74-86 ( <sup>3,33,34,45</sup> )	Not detectable <sup>c</sup> ( <sup>49</sup> )	0.4 ( <sup>49</sup> )	—	—	—	—
Cephaloridine	38 ( <sup>2,32,42</sup> )	30.4	50-80 <sup>b</sup> ( <sup>3,32</sup> )	40-64	10-30 ( <sup>2,33</sup> )	0.4-5.6 g/ml <sup>c</sup> ( <sup>50</sup> )	—	—	—	—	—
Cephadrine	10 ( <sup>37</sup> )	8.6	86 ( <sup>37</sup> )	74	8-20 ( <sup>2,37,38</sup> )	—	—	—	—	—	—
Cefamandole	20-36 ( <sup>39,51</sup> )	6-10.8	88 ( <sup>39</sup> )	26	67-74 ( <sup>39,52</sup> )	—	—	—	—	—	—
Cefoxitin	22 ( <sup>40,41</sup> )	6.2	56-110 ( <sup>2,53</sup> )	15-30	65-79 ( <sup>2,53</sup> )	—	—	—	—	—	—

<sup>a</sup>Numbers in parentheses are references<sup>b</sup>Values inferred from data at different dosages; Cephalexin not available commercially for parenteral use<sup>c</sup>Absolute concentrations rather than percentage ratio

TABLE 3

COMPARATIVE PHARMACOKINETICS OF CEPHALOSPORINS (Part II) <sup>a</sup>							
Agent	Percentage metabolized	Serum half-life (hours)		Severe renal failure	Serum half-life during hemodialysis (hours)	Dosage in adults with normal renal function	Suggested maintenance dosages for severe infections
		Normal renal function	Moderate renal failure (creatinine clearance 10-40 ml/min)				Moderate renal failure
ORALLY-ABSORBED							Severe renal failure
Cephalexin	Minimal	0.9 (33)	3-6 (34.55)	22 (36)	4-6 (55.58)	250-500 mg four times daily	250 mg every 6 hours <sup>c</sup> 250 mg every 24 hours <sup>c</sup>
Cephadrine	Minimal	0.8 (48)	—	—	—	250-500 mg four times daily	—
PARENTERAL							
Cephalothin	33 (56.59)	0.5 (33.35, 41.56)	1.1-1.8 (59)	3 → 15 <sup>b</sup> (56.59)	3 (55.59, 60)	1 g every 3 hours or 2 g every 4 hours	1 g every 4-6 hours 1 g every 8 hours
Cephapirin	40 (43.81, 62)	0.5 (43.46-48.61)	1-1.5 (62)	1.8 (62)	1.8 (3.62)	1 g every 3 hours or 2 g every 4 hours	1 g every 4-6 hours 1 g every 8 hours
Cefazolin	Minimal	1.8 (2.33, 63)	6-12 (34.63)	56 (34.63)	9 (34.63, 65)	1 g every 4-6 hours	500 mg every 6-12 hours <sup>c</sup> 500 mg every 24-48 hours <sup>c</sup>
Cephaloridine	Minimal	1.1-1.5 (2.35, 66, 67)	4 (66)	20-24 (56.66)	4 (56.65, 68, 69)	1 g every 6 hours	Should not be given
Cefamandole	Minimal	0.6-0.8 (39.51)	—	—	—	1 g every 2-3 hours	—
Cefoxitin	Minimal	0.8 (2.40, 41.48)	—	—	—	1 g every 4-6 hours	—

<sup>a</sup>Numbers in parentheses are references<sup>c</sup>First dose should be twice as great as subsequent ones (see text)<sup>b</sup>Biphasic half-life; the larger number occurs after the eighth hour

is inherently nephrotoxic when given in excessive amounts.<sup>69,85,86</sup> The effects of coexisting renal and hepatic disease on the rates of elimination of cephalosporins have not been well studied; however, it would seem prudent to reduce the dosage of drugs such as cephalothin and cephapirin to a level below that which would be recommended for the renal dysfunction alone in patients with impairment of both liver and kidneys.

Peritoneal dialysis has little effect on the pharmacokinetics of the cephalosporins; in contrast, the drugs are moderately hemodialyzable. Therefore, in treating serious infections, an additional maintenance dose (eg, 1 g cephalothin or cephapirin, 500 mg cefazolin) should be given at the end of each dialysis.

## ADVERSE REACTIONS

### Allergic Reactions

Up to 5% of individuals receiving cephalosporins experience allergic reactions.<sup>2,42,87-89</sup> These include maculopapular, morbilliform and urticarial rashes, eosinophilia, drug fever, serum sickness and, rarely, anaphylaxis. Occasional examples of reversible thrombocytopenia, neutropenia, and hemolytic anemia have been reported.<sup>41,90-94</sup>

Positive Coombs' tests are found in some 3% or more of patients treated with these antibiotics,<sup>88,95</sup> apparently for two reasons:<sup>88,92,95</sup> (a) nonspecific (nonimmune) adherence of cephalothin-protein complexes to the surface of erythrocytes; (b) binding of specific anticephalothin antibody to drug-coated red blood cells. Rarely, hemolytic anemia has supervened due to the second mechanism.<sup>92,93</sup> There is a suggestion that cephalothin-related hemolysis may occur at lower dosages and earlier in the course of therapy than that associated with penicillin.<sup>92,95</sup> Hemolysis due to either antibiotic has clearly occurred in the absence of other manifestations of drug allergy. The hematologic abnormality may persist for weeks after discontinuation of the drugs.<sup>92</sup>

Despite the frequent presence of cross-reactive antibodies in the serum of recipients of either penicillins or cephalosporins,<sup>67,96</sup> clinically-evident allergic reactions to cephalosporins occur in only 8% (range 5-15%) of penicillin-allergic patients.<sup>86</sup> Individuals with a history of immediate hypersensitivity to penicillins (anaphylaxis, giant urticaria) should probably not be given cephalosporins because a cross-reaction could be life-threatening; however, milder, delayed reactions to penicillins do not constitute a contra-indication to the administration of cephalosporins if there are other valid reasons for their use.

### Non-Allergic Reactions

*Local effects.* Other common adverse effects of the cephalosporins are related to the route of administration. Diarrhea and minor gastrointestinal upset sometimes accompany the ingestion of

cephalexin or cephradine, with no difference between the drugs in this respect.<sup>2,37,87</sup> Pain on intramuscular injection appears to be less with cefazolin and cephaloridine than with the other congeners.<sup>2</sup> A number of controlled trials comparing the frequency of phlebitis with different cephalosporins have produced inconclusive results;<sup>97,98</sup> however, cephapirin may be somewhat less irritating than other preparations when given intravenously in comparable dosage.<sup>99</sup>

*Biochemical abnormalities.* Transient increases in SGOT, SGPT and alkaline phosphatase have rarely occurred after the administration of cephalosporins.<sup>100</sup> However, we are not aware of clinically-significant liver damage produced by these drugs.

Cephalothin in high concentrations has been reported to cause a number of defects in coagulation, including: (a) an abnormality of the second wave of platelet aggregation similar to that produced by carbenicillin;<sup>101</sup> (b) defective polymerization of fibrin with prolongation of the prothrombin and thrombin time;<sup>101</sup> (c) inhibition of factor V activity *in vitro*.<sup>102</sup> These alterations appear to have little, if any, clinical significance.

*Renal toxicity.* Cephaloridine, given in high dosages to experimental animals, injures the proximal tubular cells of the kidney; cefazolin produces a much lesser degree of damage, and cephalothin, a minimal one.<sup>103,104</sup> Acute renal failure has been well recognized in patients receiving cephaloridine, especially at dosages exceeding 6 g per day,<sup>69,85,86</sup> and has occasionally been observed with other cephalosporins.<sup>105-107</sup> However, interpretation of these reports is complicated by the frequent presence of other potentially nephrotoxic factors. Pre-existing renal disease and the coadministration of furosemide may enhance the likelihood of nephrotoxicity due to the cephalosporins.<sup>108</sup> It has been stated that patients receiving gentamicin together with cephalothin have an increased risk of nephrotoxicity over that incurred from the aminoglycosides alone;<sup>109-112</sup> however, data from controlled studies in man are conflicting.<sup>113-115</sup> and trials in experimental animals give no evidence of such an interaction.<sup>116</sup> We are not convinced of a clinically-important interaction in this regard.

## THERAPEUTIC USE

The therapeutic indications for the cephalosporins are somewhat difficult to define, and there is a widespread tendency to use these drugs when penicillins would prove at least as effective. In terms of cost (Table 4) and rate of adverse reactions, the parenterally-administered cephalosporins do not differ substantially from antistaphylococcal agents such as oxacillin or nafcillin; however, several criticisms can be levied against their use in infections known to be susceptible to penicillins; (a) penicillin G, penicillin V, or ampicillin are generally more active against susceptible organisms than any

TABLE 4

COST OF CEPHALOSPORINS AND SOME OTHER ANTIBIOTICS			
Antibiotic	Tradename(s)	Dosage	Cost of One Day's Therapy (\$)
ORAL			
Cephalexin	Keflex <sup>®</sup>	500 mg four times daily	2.25
Cephadrine	Anspor <sup>®</sup>	500 mg four times daily	2.46
	Velosef <sup>®</sup>		
Oxacillin	Bactocill <sup>®</sup>	500 mg four times daily	1.39
	Prostaphlin <sup>®</sup>		
Erythromycin		500 mg four times daily	.95
Penicillin V		500 mg four times daily	.23
Ampicillin		500 mg four times daily	.53
PARENTERAL			
Cephalothin	Keflin <sup>®</sup>	12 g per day	33.50
Cefazolin	Ancef <sup>®</sup>	6 g per day	30.75
	Kefzol <sup>®</sup>		
Cephapirin	Cefadyl <sup>®</sup>	12 g per day	34.00
Oxacillin	Bactocill	12 g per day	46.32
	Prostaphlin		

cephalosporin, and are also considerably cheaper; (b) penicillins penetrate the central nervous system more readily than do cephalosporins;<sup>18,67</sup> (c) penicillins, especially penicillin G and ampicillin, are much more active than commercially-available cephalosporins against enterococci<sup>117</sup> and *B. fragilis*.

Cephalosporins are drugs of choice in few circumstances (Table 5). These include infections due to *Staphylococcus aureus*, especially in the penicillin-allergic patient, and infections due to sensitive strains of *Klebsiella*. Hospital-acquired aspiration pneumonias often contain *Klebsiella*, staphylococci and pneumococci in addition to anaerobic mouth organisms; thus, cephalosporins may provide excellent therapy for this disease. These agents are also effective against most of the organisms found in biliary tract infections (*E. coli*, *Klebsiella*, clostridia and streptococci). Cefazolin may be particularly useful in this setting because of the relatively high concentrations it produces in the bile. However, enterococci are found with sufficient frequency in biliary tract infections that we prefer ampicillin together with an aminoglycoside. In the initial treatment of bacteremia of undetermined etiology, equally good results have been obtained with any pair of the following: a cephalosporin, an aminoglycoside (e.g., gentamicin, tobramycin), or carbenicillin.<sup>114,115</sup> Cephalosporins should not be part of the combination when there is a substantial risk of central nervous system infection, enterococcal infection, or a high likelihood of *Pseudomonas* bacteremia.

Cephalosporins may provide a useful therapeutic alternative in patients allergic to penicillins (Table 5); however, they should not be given to individuals with a history of severe penicillin allergy (giant hives, anaphylaxis). Enterococcal infections respond poorly to cephalosporins and the alternative to penicillins should be erythromycin or vancomycin. Meningitis due to susceptible organisms has developed during therapy with the cephalosporins,<sup>18</sup> apparently due to poor penetration of the antibiotic into the meninges; therefore, these drugs

should be avoided in patients with central nervous system infections, or with a high risk of developing such a complication (for example, in meningococcal bacteremia). In the penicillin-allergic patient, chloramphenicol provides effective therapy of meningitis due to the pneumococcus, meningococcus, and *H. influenzae*, and erythromycin is also effective for the first two organisms. If it is elected to use a cephalosporin for some reason, the drug should be given in high dosage, and it may be prudent to administer intrathecal cephaloridine (12.5-50 mg per day) concomitantly.<sup>18</sup>

Commercially-available cephalosporins are only moderately inhibitory to *H. influenzae*; however, cefamandole appears more promising in this regard. The cephalosporins currently on the market are only weakly active against *B. fragilis* and cannot be considered drugs of choice for peritonitis or chronic pelvic inflammatory disease; cefoxitin may prove useful for these infections. Cephalosporins are accepted therapy for gonorrhea only in the pregnant, penicillin-allergic individual with acute uncomplicated genital infection.<sup>20,21,124</sup> Although cefazolin 2 g intramuscularly together with 1 g of probenecid by mouth is considered adequate in this instance,<sup>124</sup> failure rates as high as 20% have been reported<sup>126</sup> so that a course of treatment, rather than a single dose may be preferable. Cephaloridine also is fairly effective as single-dose (2 g) therapy of acute gonorrhea. One cephalosporin (cephaloridine) has been used to treat syphilis, but its efficacy is not as well-documented as that of the penicillins. Although most strains of salmonella are relatively sensitive to cephalosporins in vitro, there is evidence that cephaloridine and cephalothin are ineffective in the treatment of typhoid fever.<sup>122,123</sup> In contrast, one recent study showed cefazolin in high dosage to be effective in the therapy of this disease.<sup>125</sup> This issue must be further evaluated before a conclusion can be reached. Data are insufficient to support the value of cephalosporins in the treatment of shigellosis.

The indications for oral cephalosporins are lim-

TABLE 5

## SOME INDICATIONS AND CONTRAINDICATIONS FOR CEPHALOSPORINS

<i>A reasonable choice</i>	<i>A good alternative drug (e.g. penicillin allergy) or where indicated for other reasons</i>	<i>Efficacy not proven</i>	<i>Generally contraindicated</i>
Penicillin-resistant <i>Staph. aureus</i> especially in penicillin-allergic patient <sup>a</sup>	Most <i>Gram-positive</i> coccal infections except enterococcal	Diphtheria	Methicillin-resistant <i>Staph. aureus</i> (rare in USA)
Most <i>Klebsiella</i> infections <sup>118,199</sup> (80% sensitive)	<i>Gonococcal</i> — cefazolin may be used for penicillin-allergic pregnant patient <sup>c</sup>	Listeria	Enterococcal infections
Hospital-acquired aspiration pneumonia	Sensitive strains of <i>E. coli</i> , <i>Proteus mirabilis</i> , and other <i>Gram-negative</i> s (Investigational drugs cefamandole and cefoxitin have extended <i>Gram-negative</i> spectrum; cefamandole effective vs. <i>H. influenzae</i> (but probably not meningitis) and cefoxitin vs. <i>B. fragilis</i> )	Syphilis (cephaloridine may be effective <sup>120,121</sup> )	CNS infections
Combined with aminoglycoside (e.g. gentamicin, tobramycin) for initial therapy of undefined bacteremia <sup>b</sup>		Pelvic inflammatory disease	
		Shigellosis	
		<i>H. influenzae</i> (non-CNS) <sup>d</sup>	
	Infections due to "mouth anaerobes" (e.g. aspiration pneumonia)	Salmonellosis <sup>122-124</sup>	

<sup>a</sup>Not in patients who have had anaphylactic reaction to penicillins

<sup>b</sup>Other combinations equally effective, e.g., carbenicillin + gentamicin, carbenicillin + cephalosporin

<sup>c</sup>Should probably be given for several days, not single dose

<sup>d</sup>Cephalosporins probably effective in high dosage; cefamandole will probably prove more effective than other congeners

ited. Most urinary tract infections respond to much cheaper drugs (sulfisoxazole, ampicillin), and the majority of bacterial respiratory infections are due to organisms susceptible to ampicillin or erythromycin. Oxacillin or erythromycin are effective for soft-tissue infections due to *Gram-positive* cocci.

The cephalosporins are frequently used for prophylaxis in patients undergoing replacement of heart valves, insertion of cardiac pacemakers, implantation of orthopedic prostheses, vaginal hysterectomy and neurosurgical operations. The objective is to prevent bacterial colonization, especially by the staphylococcus. Short courses of parenteral drug given for this purpose appear to be reasonably efficacious and free of risk.<sup>127</sup>

#### CHOICE OF A CEPHALOSPORIN

There are no important differences between the two oral agents, cephalexin and cephadrine.<sup>128</sup> For intramuscular injection, cephaloridine has largely been replaced by cefazolin which is equally well tolerated, not as nephrotoxic, and because of its relatively long half-life, may be administered three to four times daily.

The cephalosporins most commonly used intravenously are cephalothin, cefazolin and cephapirin. There are no substantial therapeutic differences among these three agents;<sup>15,129</sup> however, many physicians prefer cefazolin because it is administered in a lower dosage and somewhat less frequently.<sup>3</sup> A theoretical advantage of cephalothin over other cephalosporins for serious staphylococcal infections lies in its greater resistance to staphylococcal  $\beta$ -lactamases.<sup>14</sup> There have been a few instances of failure of cefazolin in the therapy

of staphylococcal endocarditis which could possibly be related to this observation.<sup>130</sup>

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## Maine Blue Cross and Blue Shield News

### TEL-MED WELL UTILIZED

Tel-Med, the dial in health information program supported by and housed at Blue Cross and Blue Shield of Maine, has been used heavily since the reverse WATS number was installed in February.

The WATS number, 1-800-442-6385, allows Maine residents living outside of the Portland area to dial the system toll free. In February alone, 3,421 calls were received on the WATS line, and an additional 1,753 calls were received from people in the Portland dialing area.

A problem arose in February, when utilization (5,174 calls) far exceeded the previous two months combined. We found that very few people were able to reach the Tel-Med switchboard on the first try. We have now added two extra WATS lines, and we are relatively sure that over 90% of the calls to Tel-Med can now get through on the first try.

Probably due to the fact that Tel-Med is operational only during business hours, the ratio of calls from women is 3 to 1 over the number of calls from men. The tapes most frequently requested are "hypertension" (#25), "Do you want to stop smoking" (#697), "vasectomy" (#1), "tension" (#33), "bad breath" (#314), "Hiatal hernia" (#198), "bursitis or painful shoulder" (#129), "diaphragm, foam and condom" (#58), "menopause" (#173), and "masturbation" (#174).

Although the number of calls received is assurance enough that the program is being accepted by the community, we have also received a number of letters reinforcing this notion. Such comments as: "I have been sending money to (Blue Cross) for years and do appreciate this new project of yours" and "this is a fine idea and should benefit the community" came in by the dozen at the inception of the Statewide service.

A survey done in February also indicated that 30% of our non-group subscribers were aware of Tel-Med, and with the demand for brochures (over 40,000 were sent out on demand in February), the number of those aware of Tel-Med has no doubt increased since the survey.

The Tel-Med program, which was developed by the San Bernardino Medical Society, has received the active support of many members of the Maine Medical Association, and as more physicians become aware of its potential, we expect the use of the system to broaden still more in scope.

Tel-Med brochures and displays are available from: Tel-Med, 110 Free Street, Portland, Maine 04101. Please let us know how many brochures you want when you write us.

# *Program – 124th Annual Session*

## *Maine Medical Association*

**June 11, 12, 13, 14, 1977**

Arranged by the Scientific Committee

GEORGE E. DAVIS, M.D., Lewiston  
Chairman

HAROLD N. BURNHAM, M.D., Gorham

DON L. MAUNZ, M.D., Bangor



Dr. Davis

The Scientific Program of the annual meeting of the Maine Medical Association is made possible by the cooperation and assistance of the Technical Exhibitors and the following organizations:

**Maine Medical Center, Department of Pediatrics**  
Portland, Maine

**Tufts University School of Medicine**  
Boston, Massachusetts

**Merck Sharp & Dohme Postgraduate Program**  
West Point, Pennsylvania

**Maine Chapter, American Academy of Family Physicians**

**Maine Chapter, American College of Surgeons**

**Maine Medico-Legal Society**

**Maine Trauma Committee**

**Abbott Laboratories**  
North Chicago, Illinois

**Blackwell's Surgical and Orthopedic Appliances**  
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**Bristol Laboratories**  
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**tion Program**

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**Maine Blue Cross and Blue Shield**  
Portland, Maine

**Maine Pharmaceutical Association**

**Mead Johnson Laboratories**  
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**E. R. Squibb & Sons, Inc.**  
Princeton, New Jersey

**Treadway-Samoset Resort**  
Rockport, Maine

**U.S. Air Force Recruiting Detachment 109 (ATC)**  
Bedford, Massachusetts

### *Specialty Groups*

**Maine Society of Allergy and Immunology**

**Maine Society of Gastroenterology**

**Maine Society of Internal Medicine and the  
American College of Physicians**

**Maine Neurological Society**

**Maine Neurosurgical Society**

**Maine Chapter, American Academy of Pediatrics**

**Maine Psychiatric Association**

**Section on Ophthalmology of the M.M.A.**

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## **Information**

### **Registration:**

Registration throughout the session will be in the Lobby at the Treadway-Samoset.

Saturday, June 11 — 12:00 M. to 5:00 P.M.

Sunday, June 12 — 8:30 A.M. to 5:00 P.M.

Monday, June 13 — 8:30 A.M. to 5:00 P.M.

Tuesday, June 14 — 8:30 A.M. to 3:00 P.M.

**Telephone: The number at the Treadway-Samoset is Rockport, (207) 594-2511.**

### **Visiting Delegates:**

Introduction of Visiting Delegates will take place at meetings of the House of Delegates on Saturday, June 11 and Sunday, June 12.

### **Technical Exhibits:**

This year, twenty-two companies are contributing to

the success of the annual session program by participating in the Technical Exhibits. A list of the exhibiting companies and representatives will be found on page 171 of this program.

**Please show your appreciation for the support of these companies by visiting these exhibits.**

#### **Badge Code:**

Badges with green borders indicate Officers, Past Presidents, Delegates and Alternate Delegates of the M.M.A.; yellow borders, members of the M.M.A.; blue borders, guests; red borders, exhibitors; and plain white for the members of the Auxiliary.

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## **Saturday, June 11**

2:00 P.M. First Meeting of the House of Delegates

Call to Order: RICHARD C. LECK, M.D., President

Presiding: Speaker of the House, GEORGE W. BOSTWICK, M.D.

Presentation of the A. H. Robins' Physician Award for Community Service

Presentation of the Maine Blue Cross and Blue Shield "Award of Appreciation"

6:30 P.M. Cocktails (Cash Bar)

7:30 P.M. Dinner

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## **Sunday, June 12**

8:30 A.M. Reference Committee Meetings

12:00 M. Luncheon

2:00 P.M. Second Meeting of the House of Delegates

Election of President, President-elect, Executive Committee District Members and AMA Delegate and Alternate

6:30 P.M. Cocktails (Cash Bar)

7:30 P.M. Lobster Bake

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## **Monday, June 13**

### **Scientific Program**

9:00 A.M. to 12:15 P.M.

Welcome — GEORGE E. DAVIS, M.D.

**Presented by Tufts University  
School of Medicine, Boston**

### **"EXPENSIVE PROCEDURES IN DIAGNOSTIC MEDICINE"**

1. *What do they offer?*
2. *Who should order them?*

3. *Who should receive them?*

4. *Who should pay for them?*

9:00 to 9:20 A.M. STEPHEN G. PAUKER, M.D., Assistant Professor of Medicine, Tufts University School of Medicine

### **"General Background and Policy"**

9:20 to 9:40 A.M. THEODORE L. MUNSAT, M.D., Professor and Chairman, Department of Neurology, Tufts University School of Medicine

### **"CAT Scanning"**

1. *Need for (Medical Indications)?*
2. *Dangers of ?*
3. *Should GP or specialist order?*

9:40 to 10:00 A.M. RICHARD A. NORTON, M.D., Associate Professor of Medicine, Tufts University School of Medicine

### **"GI Endoscopy, Esophageal Motility Study, Fiberoptic Endoscopy of the Digestive Tract, Cannulation and Papillotomy, Laparoscopy"**

10:00 to 10:15 A.M. INTERMISSION

10:15 to 10:35 A.M. JOHN S. BANAS, JR., M.D., Associate Professor of Medicine, Tufts University School of Medicine

### **"Echocardiography, Cardiac Catheterization, Coronary Arteriography and Exercise Testing"**

10:35 to 10:55 A.M. HAROLD F. RHEINLANDER, M.D., Professor of Cardiothoracic Surgery and Professor of Surgery, Tufts University School of Medicine

### **"Surgical Procedures With Questionable Indications — Cost, Benefit Considerations"**

10:55 to 11:15 A.M. JOHN B. MCGINTY, M.D., Clinical Professor of Orthopedic Surgery, Tufts University School of Medicine

### **"Arthroscopy — Nature of the Procedure, Indications, Use and Complications"**

*(Dr. Carter will comment on each presentation from a radiologic standpoint and will participate in the Panel Discussion)*

11:15 A.M. to 12:15 P.M. Panel Discussion — all participants

*To include —*

BARBARA L. CARTER, M.D., Professor of Radiology, Tufts University School of Medicine

MR. KENNETH DOLLEY, Second Vice-President for Benefits, Union Mutual Life Insurance Company

12:00 M. LUNCHEON

## **visit the technical exhibits**

BEFORE AND AFTER EACH SESSION AND DURING INTERMISSIONS

## Scientific Program

1:45 to 4:00 P.M.

**Presented by Tufts University  
School of Medicine, Boston**

1:45 to 2:45 P.M. **Plenary Session — whole panel**

GEORGE E. DAVIS, M.D., Lewiston, Moderator

*Each participant will give one illustrative case that either did or did not need expensive tests*

2:45 to 3:00 P.M. INTERMISSION

3:00 to 4:00 P.M. **Workshops**

**"Orthopedics"** — DR. MCGINTY

**"Cardiology"** — DR. BANAS

**"GI and Surgery"** — DRs. NORTON AND RHEINLANDER

**"Neurology and X-ray"** — DRs. CARTER AND MUNSAT

7:00 P.M. **Annual Banquet**

Presentation of Honorary Pins

President's Address: RICHARD C. LECK, M.D.

Entertainment: The Robert Collier Chorale

## Tuesday, June 14

### Scientific Program

9:00 A.M. to 12:00 M.

Welcome — HAROLD N. BURNHAM, M.D.

9:00 to 10:30 A.M.

**Presented by the Department of Pediatrics  
Maine Medical Center, Portland**

**"CHILD ABUSE/NEGLECT IN THE STATE OF MAINE"**

Moderator — GEORGE W. HALLETT, M.D.

Speaker: GEORGE W. HALLETT, M.D., Chief, Department of Pediatrics, Maine Medical Center, Portland

Subject: **"When to Suspect CA/N"**

Speaker: MRS. CAROLYN MCTEAGUE, Child Protective Services Consultant, Department of Human Services, Augusta

Subject: **"What Happens After the Report?"**

Speaker: JOSEPH KOZAC, Esquire, Assistant Attorney General, Department of Human Services, Augusta

Subject: **"Legal Handling of CA/N Cases"**

Speaker: ANONYMOUS

Subject: **"A Child Abusing Mother Relates Her Feelings"**

Speaker: G. ADAIR HEATH, M.D., Child Psychiatrist, Maine Medical Center, Portland

Subject: **"Psychiatric Aspects of Abusing Parents"**

### Panel Discussion

10:30 to 10:45 A.M. COFFEE BREAK

10:45 A.M. to 12:00 M.

**"SCREENING FOR GENETIC DEFECTS IN MAINE"**

Speaker: JAMES HADDOW, M.D., Research Department, Maine Medical Center, Portland

Subject: **"Neural Tube Defects"**

Speaker: PAUL H. LAMARCHE, M.D., Chief, Department of Pediatrics, Eastern Maine Medical Center, Bangor

Subject: **"Chromosomal Defects"**

Speaker: LYMAN A. PAGE, M.D., Pediatrician, Saco

Subject: **"Hypothyroidism"**

### Panel Discussion

12:00 M. LUNCHEON

## Scientific Program

2:00 to 4:00 P.M.

Welcome — DON L. MAUNZ, M.D.

**Presented by Tufts University  
School of Medicine, Boston**

Speaker: DAVID J. GREENBLATT, M.D., Clinical Pharmacology Unit, Department of Medicine, Massachusetts General Hospital, Boston

Subject: **"Drug Interactions"**

Speaker: RUSSELL R. MILLER, Pharm.D., Ph.D., Division of Clinical Pharmacy, Department of Pharmacy, New England Medical Center Hospital, Boston

Subject: **"Modern Drug Usage"**

Speaker: ELAINE WOO, M.D., Clinical Pharmacology Unit, Department of Medicine, Massachusetts General Hospital, Boston

Subject: **"The Clinical Use of Antiarrhythmic Drugs"**

## Specialty Group Meetings

### Monday, June 13

11:00 A.M. MAINE SOCIETY OF ALLERGY AND IMMUNOLOGY

BENJAMIN ZOLOV, M.D., Portland, presiding

Business Meeting

**12:00 Noon — Main Dining Room**

**INFORMAL LUNCHEONS**

Maine Society of Gastroenterology  
Section on Ophthalmology of the M.M.A.

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**2:00 P.M. SECTION ON OPHTHALMOLOGY OF THE M.M.A.**

JOHN T. LIBBY, M.D., Portland, presiding  
Business Meeting

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**2:00 P.M. MAINE SOCIETY OF INTERNAL MEDICINE AND THE AMERICAN COLLEGE OF PHYSICIANS**

LEOPOLD A. VIGER, M.D., Biddeford and PHILIP P. THOMPSON, JR., M.D., Portland, presiding  
Business Meeting

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**4:00 P.M. MAINE NEUROSURGICAL SOCIETY AND MAINE NEUROLOGICAL SOCIETY**

RICHARD M. SWENGEL, M.D., President, Lewiston and KARL E. SANZENBACHER, M.D., President, Waterville, presiding  
Business Meeting

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**Tuesday, June 14**

**2:00 P.M. MAINE CHAPTER, AMERICAN ACADEMY OF PEDIATRICS**

GEORGE W. HALLETT, M.D., Portland, presiding  
Business Meeting

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**2:00 P.M. MAINE PSYCHIATRIC ASSOCIATION**

STEPHEN M. SOREFF, M.D., Portland, presiding  
**"Psychiatry in Intensive Care Units"**  
THOMAS P. HACKETT, M.D., Chief of Psychiatry, Massachusetts General Hospital and Professor of Psychiatry, Harvard Medical School, Boston

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**Maine Medico-Legal Society**

**Tuesday, June 14**

2:00 to 4:00 P.M.

*Presiding* — MR. JOHN R. ATWOOD, President, Augusta

**"THE PHYSICIAN'S RESPONSIBILITY TO THE PUBLIC AND THE PATIENT IN TREATING THE PATIENT/DRIVER"**

Moderator — HENRY F. RYAN, M.D., Chief Medical Examiner, State of Maine, Augusta

**Panelists:**

MR. ROBERT M. BURKE, Medical Coordinator, State Department of Motor Vehicles, Augusta

WILLIAM E. SCHUMACHER, M.D., Staff Psychiatrist, Augusta Mental Health Institute; Former Director, State Bureau of Mental Health, Augusta

GEORGE L. MALTBY, M.D., Chairman, Maine Medical Association's Medical Advisory Committee to the Secretary of State and to the Bureau of Motor Vehicles, Portland

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**Special Notices**

**A.A.F.P. Prescribed Credit**

This program is approved for 10 Prescribed Hours by the American Academy of Family Physicians.

**M.M.A. Credit for Category I**

The Monday and Tuesday regular scientific sessions are accepted for 10 hours credit (1 credit per hour) in the Physicians Recognition Award Category I.

**Executive Committee Meetings**

The Executive Committee will meet on Saturday, June 11 and daily throughout the session at a time and place to be announced.

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**HONORARY PINS**

Presentation of the Association's Honorary Pins will be made by Richard C. Leck, M.D., President of the M.M.A., at the Annual Banquet, Monday evening, June 13 at 7:00 P.M.

**FIFTY-YEAR PINS**

Fifty-Year Pins will be presented to the following members who were graduated from Medical School in 1927.

**Cumberland County**

Doris M. Sidwell-Thompson, M.D.  
University of Vermont College of Medicine

Henry M. Tabachnick, M.D.  
Tufts University School of Medicine

**Kennebec County**

L. Armand Guite, Sr., M.D.  
Cornell University College of Medicine

Howard L. Apollonio, M.D.  
Harvard Medical School

**FIFTY-FIVE-YEAR PIN**

A Fifty-Five-Year Pin will be presented to the following member who was graduated from Medical School in 1927.

Cumberland County  
Reginald T. Lombard, M.D.  
Yale University School of Medicine

### SIXTY-YEAR PIN

A Sixty-Year Pin will be presented to the following member who was graduated from Medical School in 1917.

Lincoln-Sagadahoc County  
Sidney C. Dalrymple, M.D.  
Bowdoin Medical School

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## *"Medicine Avenue"*

### Technical Exhibits

Armour Pharmaceutical Company, Greyhound Tower, Phoenix, Arizona 85077  
Representatives: Mr. George Forman, Mr. Irv Kaplan and Mr. John O'Connell

Associated Data Systems, Inc., 210 D.W. Highway South, Nashua, New Hampshire 03060

Astra Pharmaceutical Products, Inc., Pleasant Street Connector, Framingham, Massachusetts 01701  
Representative: Mr. William Sabin

Ayerst Laboratories, 685 Third Ave., New York, New York 10017  
Representatives: Mr. David Hart and Mr. Richard Souza

Boehringer Ingelheim Ltd., 33 West Tarrytown Rd., Elmsford, New York 10523  
Representatives: Mr. Al Provost and Mr. Roger Dutton

Burroughs Wellcome Company, 3030 Cornwallis Rd., Research Triangle Park, North Carolina 27709

Ciba-Geigy Corporation, Summit, New Jersey 07901  
Representative: Mr. Chuck Hamilton

Dow & Pinkham, Div. of Morse, Payson & Noyes, 57 Exchange St., Portland, Maine 04112  
Representative: Mr. Richard H. Pew, Jr.

Lederle Laboratories, Pearl River, New York 10965  
Representatives: Mr. Rocco Maffei, Mr. Scott Keniston, Mr. Ron Hayman and Mr. P. DeCotis

Maine Blue Cross and Blue Shield, 110 Free St., Portland, Maine 04101  
Representatives: Mrs. Laura Franciose, Mrs. Shirley Brochu and Mr. Ralph B. Osgood

McNeil Laboratories, Inc., Camp Hill Rd., Fort Washington, Pennsylvania 19034  
Representative: Mr. Joe Ruest

Navy Recruiting District Boston, 575 Technology Square, Cambridge, Massachusetts 02139

Pfizer Laboratories Division, 230 Brighton Rd., Clifton, New Jersey 07012  
Representatives: Mr. Charles Jankowski, Mr. Jerry Dorsky and Mr. Joe Maioriello

Respiratory Therapy Inc., 1098 Brighton Ave., Portland, Maine 04102  
Representatives: Mr. Michael Sullivan, Mr. Richard Cote, Mr. Jean Malo and Mr. Donald Chase

A. H. Robins Company, 1407 Cummings Dr., Richmond, Virginia 23220  
Representative: Mr. Albert W. Messer

Roche Laboratories, Nutley, New Jersey 07110  
Representative: Mr. Peter Davis

Ross Laboratories, 625 Cleveland Ave., Columbus, Ohio 43216

Sandoz Pharmaceuticals, E. Hanover, New Jersey 07936  
Representatives: Mr. Larry Emidy and Mr. Wayne Jackson

Searle Laboratories, Box 5110, Chicago, Illinois 60680  
Representatives: Mr. Daniel Arimento, Mr. Alfred Grimes and Mr. Thomas Ordway

Smith Kline & French Laboratories, 1500 Spring Garden St., P.O. Box 7929, Philadelphia, Pennsylvania 19101  
Representatives: Mr. Kenneth S. Mosher and Mr. Robert R. Phair

U.S.A.F. Recruiting Detachment 109 (ATC), 4 De Angelo Drive, Bedford, Massachusetts 01730  
Representatives: Captain Neil G. Patterson, MSgt Frank R. Luchart and TSgt Kenneth S. Willey

Wheel Chair Fashions, Inc., Box 99, South Windham, Maine 04082  
Representatives: Ms. Marion Adams and Ms. Charlotte Adams

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### Visiting Delegates

New Hampshire Medical Society  
THEODORE S. SMITH, M.D., Concord

The Rhode Island Medical Society  
ROBERT L. CONRAD, M.D., Wakefield

Vermont State Medical Society  
B. ALBERT RING, M.D., Burlington

## Delegates to Out-of-State Meetings

The Connecticut State Medical Society  
GEORGE W. BOSTWICK, M.D., Newcastle

The Massachusetts Medical Society  
NELSON P. BLACKBURN, M.D., Bath

New Hampshire and Vermont State Medical Societies  
ROBERT F. FICKER, M.D., Kennebunkport

The Rhode Island Medical Society  
LEONARD G. MIRAGLIUOLO, M.D., Bangor

## County Delegates

### DELEGATES

### ALTERNATES

#### Androscoggin County Medical Association

Frederick B. Lidstone, M.D., Secretary	
Charles A. Hannigan, M.D.	Margaret H. Hannigan, M.D.
Frederick C. Holler, M.D.	Jon P. Pitman, M.D.
Thomas F. Shields, M.D.	Ake Akerberg, M.D.
Jou S. Tchao, M.D.	Kenneth P. Wolf, M.D.
Behzad Fakhery, M.D.	Mary T. Dycio, M.D.

#### Aroostook County Medical Society

George J. Harrison, M.D., Secretary	
Madjid Yaghmai, M.D.	William A. O'Brien, M.D.
Michael J. Kellum, M.D.	J. B. Leith Hartman, M.D.
Arthur D. Pendleton, M.D.	Alroy A. Chow, M.D.

#### Cumberland County Medical Society

Wesley J. English, M.D., Secretary	
David L. Adams, M.D.	Martin A. Barron, Jr., M.D.
Donald P. Cole, M.D.	William J. Hall, III, M.D.
Bernard Givertz, M.D.	Theodore J. Hallee, M.D.
Walter B. Goldfarb, M.D.	John E. Knowles, M.D.
William L. MacVane, Jr., M.D.	Bruce D. Nelson, M.D.
Stephen E. Monaghan, M.D.	Alfred E. Swett, M.D.
Stanley B. Sylvester, M.D.	Robert P. Timothy, M.D.
Louis A. Ciampi, M.D.	Carl A. Brinkman, M.D.
Patrick A. Dowling, M.D.	Brian M. Dorsk, M.D.
Andrew P. Iverson, Jr., M.D.	John A. Godsoe, M.D.
John D. Kilgallen, M.D.	Michael L. Shuman, M.D.
Harold N. Burnham, M.D.	Stephen B. Paulding, M.D.
Raphael F. Turgeon, M.D.	Peter B. Webber, M.D.

#### Franklin County Medical Society

Daniel K. Onion, M.D., Secretary	
David C. Dixon, M.D.	Paul A. Brinkman, M.D.

#### Hancock County Medical Society

William C. Bromley, M.D., Secretary

### DELEGATES

### ALTERNATES

Winston G. Stewart, M.D.	Larry R. Williams, M.D.
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#### Kennebec County Medical Association

Oscar T. Feagin, M.D., Secretary	
Earle M. Davis, M.D.	John H. Shaw, M.D.
James C. Hayes, M.D.	Martyn A. Vickers, Jr., M.D.
Richard E. Barron, M.D.	George I. Gould, M.D.
John W. Towne, M.D.	Peter J. Leadley, M.D.
Gareth O. M. Jones, M.D.	Joseph J. Hiebel, M.D.
Valentine J. Moore, M.D.	Howard H. Milliken, M.D.
Raymond E. Culver, M.D.	Meyer Emanuel, M.D.

#### Knox County Medical Society

Jack D. McCue, M.D., Secretary	
David G. Reed, M.D.	Peter R. Shrier, M.D.
Christopher F. Manning, M.D.	Gordon T. Paine, Jr., M.D.

#### Lincoln-Sagadahoc County Medical Society

George W. Bostwick, M.D., Secretary	
Gilbert R. Rowan, M.D.	Paul H. Dumdey, M.D.
David W. Schall, M.D.	Richard Evans, III, M.D.

#### Oxford County Medical Society

Sidney M. Schnittke, M.D., Secretary	
Harry L. Harper, M.D.	
H. Richard Bean, M.D.	

#### Penobscot County Medical Society

H. Clement Jurgeleit, M.D., Secretary	
John J. Pearson, M.D.	Sidney Chason, M.D.
Robert P. Andrews, M.D.	G. Douglass Timms, M.D.
Francis I. Kittredge, M.D.	Parker F. Harris, M.D.
Carroll P. Osgood, Jr., M.D.	James R. Curtis, M.D.
Leonardo L. Leonidas, M.D.	John F. Adams, Jr., M.D.
Jack N. Meltzer, M.D.	Allison K. Hill, M.D.
David S. Beebe, M.D.	Don L. Maunz, M.D.

#### Piscataquis County Medical Society

James W. Berry, M.D., Secretary	
Charles H. Lightbody, M.D.	

#### Somerset County Medical Society

John H. Steeves, M.D., Secretary	
Harland G. Turner, M.D.	Richard C. Taylor, M.D.

#### Waldo County Medical Society

Joseph A. Smith, M.D., Secretary	
T. Craig Childs, M.D.	

#### Washington County Medical Society

Karl V. Larson, M.D., Secretary	
Robert G. MacBride, M.D.	Donald M. Robertson, M.D.

#### York County Medical Society

Melvin Bacon, M.D., Secretary	
Robert F. Ficker, M.D.	Thomas Anton, M.D.
Carl E. Richards, M.D.	Michael J. Festino, M.D.
Michael M. P. Magaouda, M.D.	Alvin A. Hoffman, M.D.

## DRUG THERAPY REVIEWS — Antimicrobial Spectrum, Pharmacology, and Therapeutic Use of Antibiotics: III. Cephalosporins — Continued from Page 165

- tics in a typhoid model. Antimicrob Agents Chemother — 1966, pp 6-10.
123. Steinbrunn, W., Haemmerli, U. P.: Clinical trials of cephalothin, a new antibiotic. Ger Med Mon 12: 170-174, 1967.
  124. Uwaydah, M.: Cefazolin in the treatment of acute enteric fever. Antimicrob Agents Chemother 10: 52-56, 1976.
  125. Center for Disease Control: Gonorrhea: recommended treatment schedules. Ann Intern Med 82: 230-233, 1975.
  126. Duncan, W. C.: Treatment of gonorrhea with cefazolin plus probenecid. J Infect Dis 130: 398-401, 1974.
  127. Tally, F. P., Gorbach, S. L.: Antibiotics in surgery. Adv Surg 9: 41-95, 1975.
  128. Mogabgab, W. J.: Comparison of cephradine and cephalexin in the treatment of respiratory and urinary tract infections. Curr Ther Res 19: 421-432, 1976.
  129. Jackson, G. G., Riff, L. J., Zimelis, V. M., et al: Double-blind comparison of cephacetrile with cephalothin/cephaloridine. Antimicrob Agents Chemother 5: 247-254, 1974.
  130. Bryant, R. E., Alford, R. H.: Unsuccessful treatment of staphylococcal endocarditis with cefazolin. JAMA 237: 569-570, 1977.

# News, Notes and Announcements

## 1977 Continuing Medical Education

### Summer Seminars

#### Colby College, Waterville, Maine

June 11-August 19 — The 32nd Annual Lancaster Course in Ophthalmology

June 25-26 — Third Seminar in Audiology

July 10-13 — 4th Annual Topics in Clinical Hematology

July 14-17 — 3rd Annual Topics in Clinical Oncology

July 17-20 — 1st Annual Seminar in Pediatrics

July 19-22 — 7th Annual Seminar in Surgical Techniques

July 24-28 — 8th Annual Seminar in Neurosurgical Techniques

July 27-30 — 1st Annual Seminar in Epilepsy

July 31-August 3 — 18th Annual Seminar in Otolaryngology

August 3-6 — 1st Annual Seminar in Dermatology

August 7-11 — 3rd Annual Seminar in Ophthalmology

August 14-18 — 1st Annual Seminar in Occupational Medicine

August 14-19 — 9th Annual Seminar in Nuclear Medicine

August 21-24 — 4th Seminar in Forensic Medicine

August 21-25 — 4th Seminar in Pulmonary Disease

## Physician Preceptors Needed

If serving as a preceptor to a medical student this summer interests you, please write to Donna M. Knightly, Assistant Project Director, Medical Care Development, Inc., 295 Water Street, Augusta, Maine, or call 622-7566. Students in their pre-clinical, third, or fourth year are available during July and August. Limited funding possible. Your earliest response will be appreciated.

## Maine Medical & Hospital Malpractice

### Joint Underwriting Association

#### Physicians and Surgeons

#### Introduction

The Joint Underwriting Association was created by Act of the Maine Legislature (Chapter 442 of the Public Laws of 1975).

The members of the Association are all insurers authorized to write and engaged in writing personal injury liability insurance in Maine. Insurers with total assets less than \$5,000,000 are not required to be members.

The purpose of the Association is to provide a temporary market for medical malpractice insurance on a self-supporting basis without subsidy from its members.

The Association is governed by a board of eleven directors, eight of whom are elected by its members. Three directors are appointed by the Superintendent of Insurance of the State of Maine. Two of the appointed directors represent the Maine Medical Association and one represents the Maine Hospital Association.

#### Stabilization Reserve Fund

The same act which created the JUA also created a Stabilization Reserve Fund administered separately by its own board of three directors. Its revenues come from a surcharge equal to 1/3 of the regular JUA premiums. All monies received by the Fund are held in trust by a bank selected by the Directors of the Fund. The Stabilization Reserve Fund is available to pay obligations of the JUA should premiums prove inadequate. If any money remains in the Fund, it will be returned to the policyholders.

#### Who Provides the Service

The Association entered into a contract with the St. Paul Fire and Marine Insurance Company in which the St. Paul has agreed to be the servicing carrier and administrator. All business will be transacted in the name of the Association by the St. Paul, which is one of the nation's most experienced underwriters of liability insurance in the health care field.

#### How to Effect Coverage

An application must be completed in detail and be signed by the applicant. It should then be mailed to the JUA at P.O. Box 9147, J.F.K. Station, Boston, Mass. 02114. The Portland, Maine

telephone number, (207) 775-3033 is connected directly with the office in Boston. A quotation will be furnished within 10 working days of receipt of the application. *Coverage can become effective no earlier than 12:01 a.m., one day after the JUA receives the premium.*

#### What Limits and Coverages are Available

The maximum limits of liability for professional coverage are \$1,000,000 each claim, \$3,000,000 annual aggregate. Any combination of limits can be purchased up to the maximum. The coverage form is the ISO form and is written on the occurrence basis.

Office premises liability coverage is not available. Only professional coverage can be purchased.

#### How are Premiums Paid

Upon receipt of the quotation the producer should collect the premium from the applicant. The producer should then send a check payable to the Joint Underwriting Association for the net premium after deducting commission. The commission is 4%.

In addition to the premium the insured is required to make a payment to the Stabilization Reserve Fund of an amount equal to 1/3 of the premium. No commission is payable on this amount and it should be included in the check payable to the JUA.

Producers are responsible for return commissions in event of return premiums. *Note again that coverage cannot become effective until 1 day following receipt by JUA of the premium.*

#### Who to Contact for Information

The following persons should be contacted for further information:

Chester A. Dossall, CPCU

MANAGER

Gerald J. Cassidy

Manager, Claim Department

Sandra A. Hayden, R.N.

Manager, Loss Prevention

Nancy M. Kenney, CPCU

Manager, Underwriting Department

The address and telephone numbers are:

P.O. Box 9147 — JFK Station

50 Staniford Street

Boston, Massachusetts 02114

Portland, Maine 207-775-3033

Boston, Massachusetts 617-742-5070

#### What are the Classifications and Rates

The JUA is using the manual published by the Insurance Service Office. Please refer to that manual for guidance. Final classification and rates can only be determined by the JUA after receipt of a completed and signed application.

## New "Journal of Clinical Engineering" Introduced

By special arrangement, interested readers of this publication may receive, without charge, a single complimentary copy (value \$8) of the new *Journal of Clinical Engineering*. This new quarterly journal is published by Quest Publishing Co., and edited by Morton D. Schwartz, Ph.D., P.E. The Premier Issue, just released, contains articles on: hospital instrumentation services; technical work in clinical engineering; costs of clinical engineering services; career opportunities for Biomedical Equipment Technicians (BMETs); and, professional certification versus registration for clinical engineers (CEs) and BMETs. Interesting departments include the "Forum," where local and regional CE and BMET groups communicate their activities, and "Technology and Trends," which features new health-care technology. A Directory of local and regional CE and BMET organizations is included. According to Dr. Schwartz, "The new *Journal of Clinical Engineering* is devoted to serving the day-to-day technical and professional information needs of biomedical engineers, clinical engineers, BMETs, hospital personnel, and all who work with clinical technology." A complimentary copy may be requested from: Mrs. Charlene Whitney, Quest Publishing Co., P.O. Box 4141, Diamond Bar, California 91765.

# County Society Notes

## Androscoggin

The monthly meeting of the Androscoggin County Medical Society was held at Steckino's Restaurant in Lewiston, Maine on December 16, 1976. The meeting was opened by the President, Dr. Stanley D. Rosenblatt, at 7:55 p.m.

Dr. Rosenblatt introduced the President of the Maine Medical Association, Dr. Richard C. Leck, who spoke on the meeting of the Delegates held the past Sunday at Waterville. In Dr. Leck's talk he recommended that:

1. One member be assigned to each Legislator. He urged coordination of efforts regarding Legislation.

2. The matter of Public Relations related to transfer of patients from one doctor to another, especially if the patient owes doctor money.

3. Dr. Leck urged doctors to sign death certificates if one of our patients dies, especially when patient is in a nursing home.

4. National Legislation is being considered to certify paramedical personnel as well as Doctor's re-certification.

5. Doctors in Bangor are suing Commissioner Smith regarding payment for use of CAT Scanner.

Dr. Thomas F. Shields expressed his views on malpractice insurance. He raised the question of self insurance.

Dr. Rosenblatt dispensed with the minutes of last meeting.

Three applications for membership were reviewed, accepted and elected to membership: Drs. James Hoffmeister, Donald Morgan, and Robert Sylvester transferred from Cumberland County to Androscoggin. All were welcomed to membership into the Androscoggin County Medical Association.

Dr. Lawrence A. Nadeau read a tribute to the late Dr. John T. Konecki. It was voted to accept this resolution and make it part of the record of this meeting. A copy will be sent to the family and to the Maine Medical Association.

Dr. Louis N. Fishman reported for the Nominating Committee. Officers nominated and elected were:

President: Dr. Charles A. Hannigan, Lewiston

Vice-President: Dr. Jou S. Tchao, Lewiston

Secretary-Treasurer: Dr. Frederick B. Lidstone, Auburn

Councilor: Dr. Stanley D. Rosenblatt, Lewiston

Delegate to the M.M.A. House of Delegates: Dr. Frederick C. Holler, Lewiston. Alternate: Dr. Ake Akerberg, Lewiston

Dr. Ross W. Green was nominated and voted Councilor to replace Dr. Cyprien L. Martel, Jr. at the end of his term in June to M.M.A. District 7.

A letter of appreciation will be sent to Dr. Richard M. Swengel for his excellent services as Secretary-Treasurer the past years.

The next meeting is to be held at NO TOMATOES, 36 Court St., Auburn. It is to be the meeting of the Corporators to comply with Internal Revenue Recommendation as Tax Exempt Organization.

FREDERICK B. LIDSTONE, M.D., *Secretary*

## Cumberland

The 407th meeting of the Cumberland County Medical Society was held at Valle's Steak House on November 18, 1976.

The business meeting convened at 8:00 p.m. with Vice-President Dr. Clement A. Hiebert presiding.

Applications for Membership — second reading: Drs. Michael G. Batt, Internal Medicine and Bruce R. Cassidy, Ophthalmology.

### Old Business:

1. Harvest Supper Band — the additional \$40.00 needed to completely pay for the expense of the band at the Harvest Supper was voted to the Woman's Auxiliary.

2. Annual High School Scholarship Fund — after some discussion, the matter was tabled.

3. Bylaw Change — the bylaw change relative to affiliate membership suggested at the last meeting and included in the Executive Committee and Society minutes last month was passed unanimously.

### New Business: none

Dr. Douglas Hill discussed the outcome of the Malpractice

Commission Hearing at the Law School on November 15, 1976.

Mr. Joe Bradley of MEDCU presented a program on the services provided by MEDCU and some of the rules that govern the use of MEDCU. The program was well-received and very informative.

The meeting was adjourned at approximately 9:15 p.m.

WESLEY J. ENGLISH, M.D., *Secretary*

## Franklin

The Franklin County Medical Society met on December 6, 1976.

Presiding at the meeting was the President, Dr. Paul A. Brinkman.

Dr. Brinkman announced that a County Society supper evening meeting would be held at the Colony Restaurant, Monday, January 24. Wives have been invited. Dr. Robert E. McAfee and Dr. David L. Phillips will be the speakers.

Drs. Roderick Prior, John Roach, Page Sharp, Jr., Daniel Barnett and Jeffrey Poole were elected to membership in the County Society.

DANIEL K. ONION, M.D., *Secretary*

## Hancock

A reorganization meeting of the Hancock County Medical Society was held on December 8, 1976 at the Tidewater Lodge, Trenton, Maine. Twenty-two doctors and several wives attended.

Elected officers for the coming year are:

President: Dr. John D. McIntyre, Ellsworth

Vice-President: Dr. John R. Tyler, Blue Hill

Secretary-Treasurer: Dr. William C. Bromley, Ellsworth

Delegate to the M.M.A. House of Delegates: Dr. Winston G. Stewart, Bar Harbor. Alternate: Dr. Larry R. Williams, Castine

A brief business meeting followed a convivial dinner. Membership forms were distributed to several new physicians in the county. A scientific presentation by Dr. P. Maynard Beach on the anatomy of physiology of respiratory impairment in serious chest injuries was well received.

BRADLEY E. BROWNLOW, M.D., *Secretary pro tem*

## Kennebec

A meeting of the Kennebec County Medical Association was held at the Holiday Inn in Augusta, Maine on November 18, 1976.

The meeting was called to order by the President, Dr. James C. Hayes at 8:05 p.m. following a delicious repast of roast prime ribs of beef. Thirty members were in attendance.

Minutes of the previous meeting were read and approved.

Under correspondence, the only communication was a massive document from Mr. Cragin representing the testimony he gave to the Malpractice Commission. Some pertinent points about this were read by the Secretary.

There was no old business.

### New Business:

Dr. Ulrich Jacobsohn mentioned the Grand Round meetings at the Augusta Mental Health Institute which would be for category one credit on every other Tuesday, and Dr. B. Lincoln Wales, Jr. communicated an appeal for a volunteer in the community about the Swine Flu clinics. Following this, Dr. Hayes introduced Dr. Robert Wise who spoke to the Association on antibiotic utilization and infectious diseases and gave a most useful presentation with considerable degree of interest on the part of the members present.

The Kennebec County Medical Association met at the Silent Woman Restaurant in Waterville, Maine on December 16, 1976 with 28 members and two guests in attendance. Following the cocktail hour and a very nice steak dinner, the meeting was called to order by the President, Dr. James C. Hayes, at 8:00 p.m.

The minutes of the November meeting were read and accepted.

**Correspondence:** The endorsement of the Secretary of the Pueblo Medical Society for Dr. Charles Meredith was read. A letter from the Maine Medical Association regarding the selection of delegates to the State Society was read and Dr. Hayes appointed a Committee of Drs. Gould, Mohlar and Davis to nominate a panel of delegates.

**New Business:** None

Ms. Cynthia Hilton, the legislative assistant to Congressman William Cohen, spoke to the Association about the process for legislation in the upcoming Congress. She reviewed the situation of the last Congress and following her presentation, a very enjoyable discussion period was held in which the members of the Association seemed to be both amazed and informed relative to the legislative process.

The Council of the Kennebec County Medical Association met at the Holiday Inn at Augusta, Maine on January 6, 1977 with all members in attendance.

The report of the nominating committee on the delegates to the Maine Medical Association was read. Some discussion followed as to whether the Members of the Council should all be delegates, and this will be brought up at the next meeting of the Association.

The second item of business was the request by Dr. Darlington for identification of key men to approach the legislators in the Waterville area. Dr. Towne and Dr. Moore were able to supply several names and will work on the others.

The third item of business was the question of a local county newsletter and Dr. Feagin stated that he would attempt to do something along these lines.

The fourth item of business was a complaint regarding one of the members. There was considerable discussion of this and it was felt that the question had pretty well been resolved by the Doctor's response.

The fifth item was a request of one of the members for affiliate status and the Council felt that this should not be given as we do not have any good reason for such.

Considerable discussion then ensued regarding the relationship of the County Association with the State Society and it is anticipated that possibly some resolutions will be forthcoming for consideration at the next State Society meeting.

O. THOMAS FEAGIN, M.D., *Secretary*

### Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at the Ledges in Wiscasset, Maine on November 16, 1976.

There were thirty-four members and guests present.

The meeting was called to order by the President, Dr. David S. Hill, at 8:40 p.m.; the minutes of the October meeting were read by the secretary and accepted.

The Board of Censors proposed the name of Dr. Peter Haughwout, of Brunswick, to active membership. This recommendation was accepted without dissent.

Dr. Bostwick announced that the M.M.A. nominating committee is looking for candidates for State committees, and also that the office of District #3 representative to the Executive Committee will be open in June. This County Society and the Knox County Medical Society must vote on a nominee by January. Dr. Leck discussed the job description for such a representative.

The annual meeting will be held in December. Dr. Hill appointed Drs. David W. Schall, Frank O. Avantaggio, Jr. and Charles E. Burden to the nominating committee to bring in a slate of officers for 1977.

There was no other new business. Dr. Paul H. Dumdey introduced the speaker, Dr. Hugh P. Robinson, of Portland, who spoke on Urologic Trauma.

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges Inn in Wiscasset, Maine on December 21, 1976.

There were thirty-five members and guests present.

The meeting was called to order, after dinner, at 8:50 p.m. by President Hill. The minutes of the last meeting were read and accepted as read. The report of the Nominating Committee was accepted, as amended by vote, and the following officers were

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elected:

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Vice-President: Dr. Aldo F. Llorente, Brunswick

Secretary-Treasurer: Dr. George W. Bostwick, Newcastle

Delegates to the M.M.A. House of Delegates: Drs. Gilbert R. Rowan, Bath and David W. Schall, Brunswick. Alternates: Drs. Paul H. Dumdey, Bath and Richard Evans, III, Brunswick

Censors: Drs. Samuel L. Belknap, Damariscotta, Carl R. Griffin, Jr., Boothbay Harbor and Elihu York, Brunswick  
Program Committee: Drs. Frank O. Avantaggio, Jr., Damariscotta and William G. Wilkoff, Bath

The secretary then read a letter from M.M.A. requesting names of physicians who could make contact with State legislators. Several volunteered.

The membership voted to submit the name of Dr. Anthony J. Horstman to the M.M.A. Nominating Committee as the official county choice for representative of District #3 on the M.M.A. Executive Committee, to succeed Dr. Wickenden in June 1977. Dr. Horstman has agreed to serve if elected by the M.M.A. House of Delegates. Other business was postponed until the January meeting, and the Program Committee introduced Dr. Newell A. Augur, Jr., who spoke on Liver Disease.

GEORGE W. BOSTWICK, M.D., *Secretary*

## Penobscot

The November meeting of the Penobscot County Medical Society was held on November 16, 1976 at the Helm Restaurant in Bangor, Maine.

The meeting was opened by the President, Dr. John A. Woodcock and the minutes of the previous meeting discussed and approved.

Under old business, the correspondence to Governor Longley regarding the Society's concern over the proposed closing of Bangor Mental Health Institute was read including the Governor's reply of October 28, 1976; the Society is waiting further correspondence from Commissioner George Zitnay of the Department of Mental Health and Corrections. Dr. Merriam's report of the Medical-Media Liaison Committee Meeting on November 10, 1976 at the Bangor Daily News was read and discussed.

The question of prorating the County Society dues similar to the present schedule of the M.M.A. was considered. As this would require a change in bylaws, one month's notice of this question was given. It was moved and seconded that we vote on this question at the next monthly meeting in December.

It was announced to the Society that the Standing Committees of the M.M.A. for 1977-1978 will be formed in the next several months, and that members of the County Society interested in serving on one or more of these committees should notify the secretary by early December.

It was also announced that Dr. Merriam's seat on the Executive Committee (from District 8) expires in 1977. The County Society is to submit candidate(s) for his replacement by February 1977. As District 8 includes Piscataquis County, their Society will also be contacted to submit a candidate. Final nomination will be within the next two months.

Dr. Carroll P. Osgood, Jr.'s application for membership in the County Society was presented and unanimously approved.

Following the business meeting, Dr. Whitehead, Secretary of the New Brunswick Medical Society, presented a most informative and stimulating talk concerning the health care system in New Brunswick and Canada as a whole. The history of the current medicare system in Canada was outlined, explaining its present form of universal coverage with uniform fee schedules and federal cost sharing arrangement. The plan has produced an increased availability of medical care, better physician distribution, and an increased average income of physician income without alternation of doctor-patient relationships.

Some points of dissatisfaction were noted, specifically in subspecialty physician fee schedules and assessment rules regarding multiple physician involvement in the care of a particular patient. The Canadian Medical Protective Association was noted to be very effective in its legal defense of physicians at a very low cost. A question and answer period following the talk brought out

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further interesting points of the Canadian System.

As there was no further business, the meeting was adjourned.

The December meeting of the Penobscot County Medical Society was held on December 21, 1976 at the Red Lion Restaurant in Bangor, Maine.

The meeting was opened by the President, Dr. John A. Woodcock and the minutes of the previous meeting discussed and approved.

Under old business, a reply from Mr. George Zitnay, Commissioner of the Department of Mental Health and Corrections, to our October correspondence regarding the BMHI was read. He noted that our feeling in favor of retaining the Institute would be taken into consideration.

After discussion with Piscataquis County Officers, it was decided to propose Dr. Charles H. Lightbody to represent District 8 on the Executive Committee of the M.M.A. beginning in 1977.

Dr. Thornton W. Merriam, Jr. reported on the recent House of Delegates Meeting on December 12, 1976. The two Resolutions, the first, that regarding President of the M.M.A., was unanimously approved; the second, that regarding improvement of perinatal facilities in the State of Maine was not voted upon — action was deferred to our January meeting.

A letter from Emily Lane to the County Medical Society President was read and discussed. This concerned cleft lip and cleft palate facilities in the State. The described acute lack of such facilities was not shared by the membership; an acknowledgment letter is to be sent to Mrs. Lane.

A change in the County Society Bylaws was unanimously approved; to prorrate the dues after April 1st of the fiscal year and exempt dues after October 1st — on a similar basis as M.M.A. dues.

The receipt of AMA Practice Management article was acknowledged.

The correspondence from Dr. Brinton T. Darlington of December 13, 1976 regarding physician assignment to individual state legislators was discussed. Action on this is pending.

Dr. Vance A. Aloupis application for membership in the County Society was presented and unanimously approved.

Dr. Shubert moved that the County Societies augment their administrative staff with the hiring of semi-retired or retired physicians to act in an advisory capacity to better inform the M.M.A. of the particular needs and problems in the Counties. This motion was amended by Dr. Merriam to be presented as a resolution to the next House of Delegates Meeting in April 1977. Dr. McEvoy moved to refer the entire motion to the Executive Committee. This was unanimously passed.

Following the business meeting, Dr. Bradley E. Brownlow of the Maine Health Systems Agency presented a most informative talk concerning the new socio-political organization of Health System Agencies that will affect us all in the control of health service and planning in the State. The organization is far more complex than much of the membership realized. Dr. Brownlow did an excellent job in hitting the key features of the program and the hierarchy of control. An interesting question and answer period followed.

As there was no further business, the meeting was adjourned at 10:00 p.m.

H. CLEMENT JURGELEIT, M.D., *Secretary*

#### Waldo

The quarterly meeting of the Waldo County Medical Society was held at Jed's Restaurant in Belfast, Maine on December 8, 1976.

Members present: Drs. Hanbury, Jollie, Knuuti, Caswell, Smith and Childs.

Election of Officers for 1977:

President: Dr. Euclid M. Hanbury, Jr., Belfast

Secretary-Treasurer: Dr. Peter M. Jollie, Belfast

Delegate to the M.M.A. House of Delegates: Dr. T. Craig

Childs, Belfast. Alternate: Dr. Joseph A. Smith, Camden

Dr. Richard C. Leck, President of the Maine Medical Association, attended as guest speaker and discussed pertinent issues to be brought up at the House of Delegates Meeting later this month.

Members will be notified of the time and location of the Spring Meeting at a later date.

PETER M. JOLLIE, M.D., *Secretary*

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## Petit Mal Status Epilepticus in a Pregnant Adult

FRANCES M. DYRO, M.D.\*

### ABSTRACT

**A twenty-eight-year-old diabetic primipara in the fifth month of pregnancy was admitted to the hospital in a confused state. Studies failed to reveal metabolic derangement as the cause of her altered state of consciousness. An electroencephalogram revealed the cause of her confusion to be petit mal status epilepticus which responded rapidly to anticonvulsants.**

### CASE REPORT

C. B., a twenty-eight-year-old right-handed teacher in the fifth month of her first pregnancy, was brought to the Maine Medical Center Emergency Room on 12/16/74. According to her husband, the patient had been diagnosed as having diabetes mellitus at the Joslin Clinic in 1951. She had been treated with insulin since that time and had been under fairly good control. The day prior to admission she had been mildly confused. Her husband thought that she was having an insulin reaction and gave her a large breakfast. On the morning of her admission, she awoke confused, not knowing time or place. Because of this continued confusion, her husband thought she needed further evaluation.

Initially, in the Emergency Room, the patient was given 50 ml of 50% glucose. No change in her mental state was noted. A blood glucose drawn prior to the injection of glucose was reported to be 294 mg%. During this time, the patient was able to answer simple questions but could not do serial seven subtractions. She did not know what subject she taught and did not know the date. She was admitted with the diagnoses of diabetes, pregnancy and question of psychiatric problems.

The question of a toxic-metabolic encephalopathy prompted the performance of an electroencephalogram on the day of admission. The record obtained on 12/16/74 is shown in Figure 1. The EEG showed continuous discharges of three to four per second spike and wave activity typical of "petit mal" or absence attacks. During the performance of the EEG, the technicians were able to carry on a conversation with the patient even though she seemed drowsy and was not always responding appropriately. At no time did she manifest any sort of overt seizure activity.

Laboratory studies during the hospitalization revealed blood glucose levels ranging from 112 to 410 mg%. BUN was 27 mg%.

potassium was 5.0 mEq/l, chloride was 102 mEq/l, sodium was 133 mEq/l.

A review of the patient's early medical history revealed that she had been evaluated at age seven because of a history of "peculiar seizures" never resembling absence attacks but rather episodes of irritability. These episodes were felt to be related to hypoglycemia. An electroencephalogram done on the patient at age seven showed "an extremely unstable pattern. A definitely abnormal tracing with many high amplitude paroxysmal bursts of three per second spike and dome patterns." The EEG was felt to be consistent with epileptic dysrhythmia. She was seen by Dr. William Lennox who was not able to elicit a history suggestive of petit mal or absence attacks. He nonetheless started her on phenobarbital which she continued to take until 1969. Although she had no further incidence of her seizure-like episodes, a followup EEG on 1/28/74 showed a single burst of fast spike and wave discharges (Figure 2).

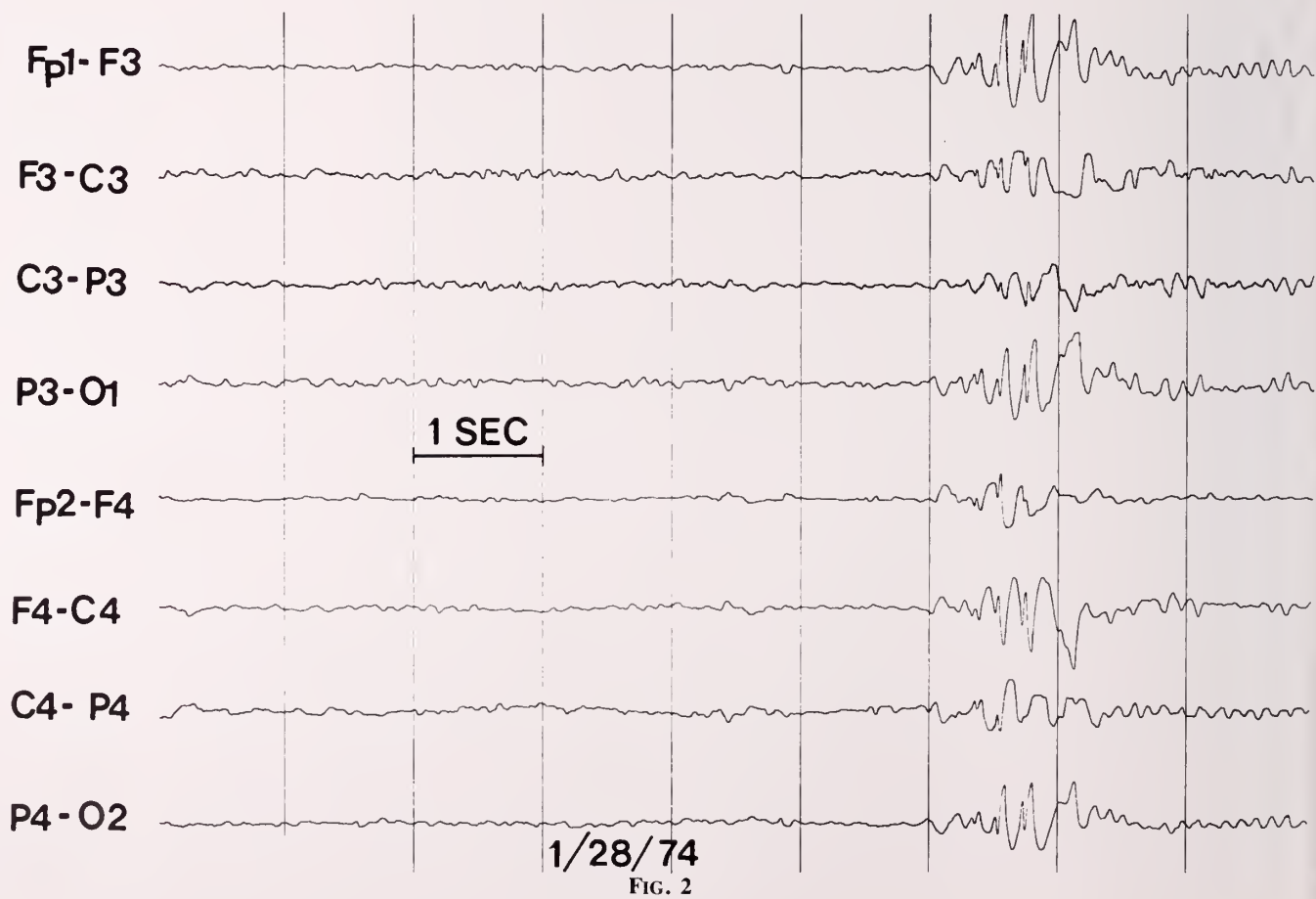
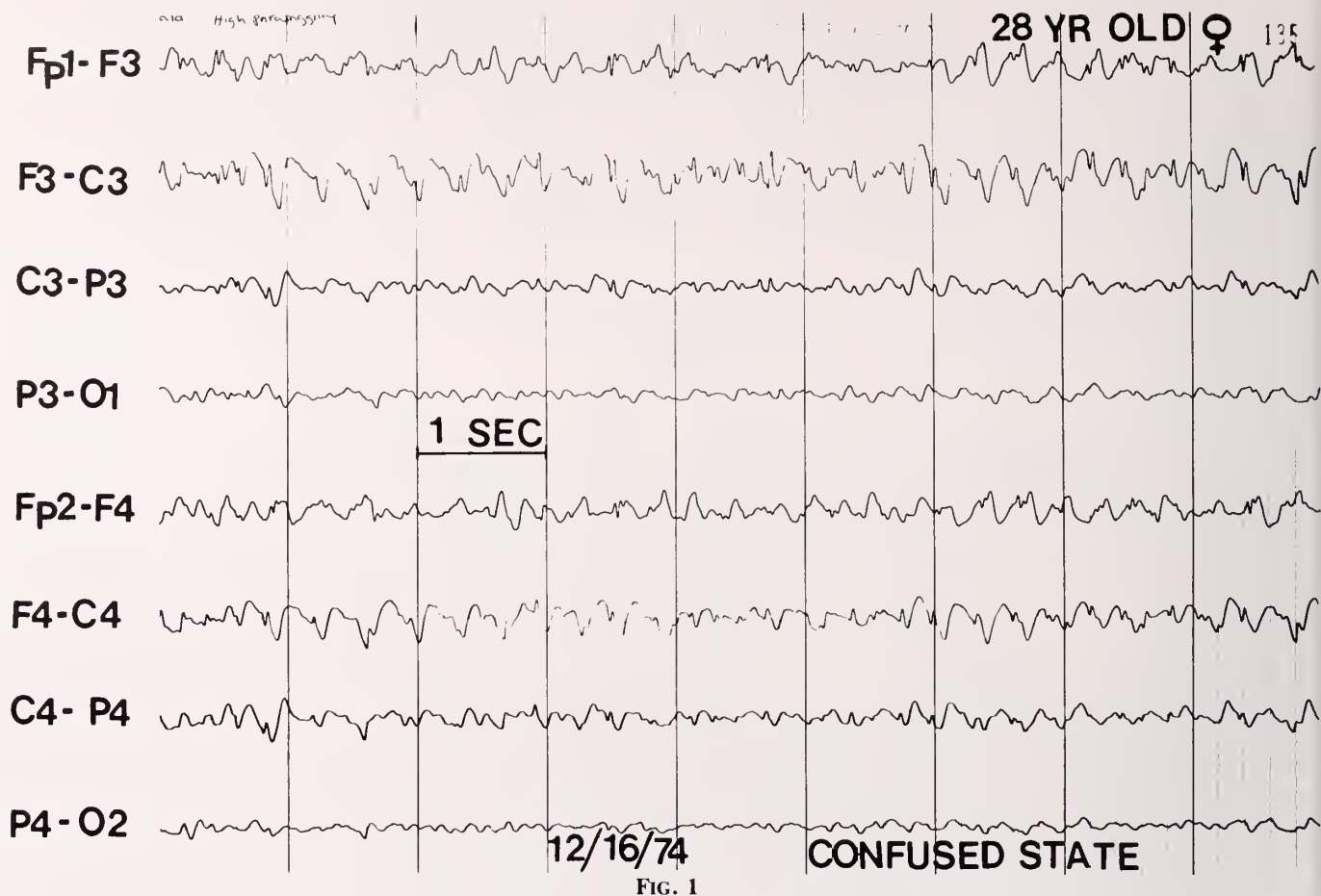
When the EEG abnormality was recognized, the patient was started on anticonvulsants. The drug of choice is diazepam but because the patient had begun to improve spontaneously, she was started on diphenylhydantoin 300 mg/day and phenobarbital 30 mg QID. She showed dramatic change in her level of awareness. A repeat EEG on 12/19/74 also showed dramatic improvement in that occasional sharp waves were seen anteriorly but background activity was essentially normal (Figure 3). The patient did fairly well in spite of a urinary tract infection. She was delivered by Caesarean section of a normal male on 3/9/75. There have been no consequent neurological problems.

### DISCUSSION

Petit mal status has been described by Schwab<sup>1</sup> as being absence attacks in rapid chains of confusion without return of full levels of consciousness associated with more or less persistent three to four cycle per second spike and slow wave abnormalities in the EEG. Petit mal status in children or adults is uncommon. Absence or petit mal seizures were typically staring spells lasting several seconds in children usually but not always without other types of seizures. There is often family history of absence attacks and seizure frequency generally decreases considerably after puberty.

Petit mal status especially in adults was thought to

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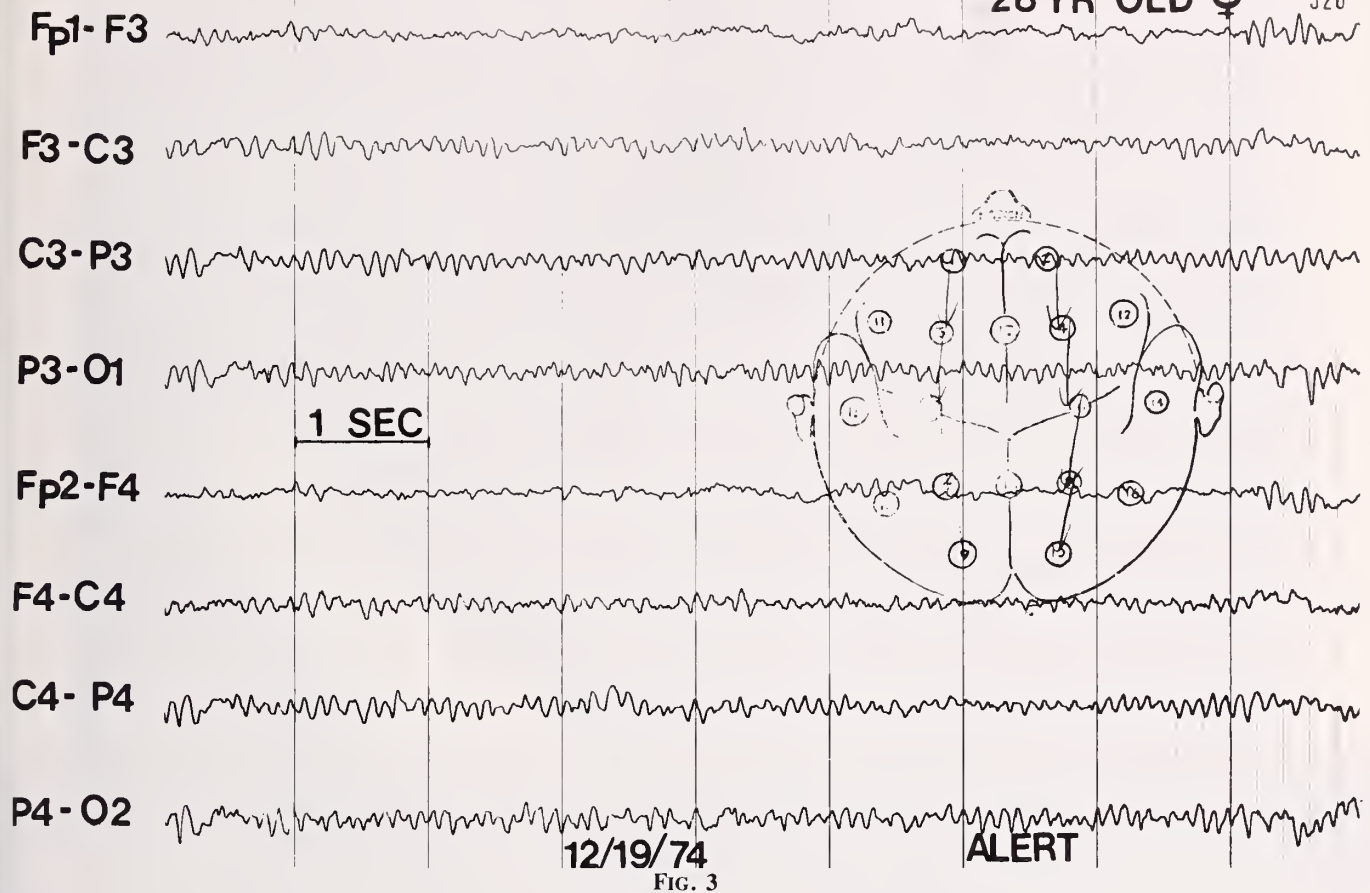


FIG. 3

be quite rare. There had been only forty cases reported in the English literature prior to 1968. Petit mal seizures rarely present *de novo* in middle age but this has been described by Schwartz and Scott.<sup>2</sup> Even in patients with known petit mal seizure disorder only three percent will ever have a prolonged episode of repetitive seizures without full return of consciousness (Gibbs and Gibbs<sup>3</sup>). In petit mal status, the patient frequently presents with confusion, amnesia, automatic and sometimes bizarre behavior. Psychiatric disturbance is frequently suspected. Mental state can vary from drowsy to groggy to dazed or confused. Occasionally patients are described as catatonic. Episodes may last from a few minutes to a week or more. Lipman, et al<sup>4</sup> were able to locate one case of petit mal status in pregnancy and another patient with petit mal status during a hyperinsulin state. Hypoglycemia is well known as a precipitating factor in any type of seizure disorder. Metabolic disorders may precipitate status epilepticus. An example is hypocalcemia.

EEG abnormalities in diabetic acidosis have been reported by Koons and Richards<sup>5</sup> who had a patient with continuous high voltage seizure-like activity with clinical confusion. In acidosis, the level of consciousness changes and clears slowly. Hypoglycemia induces increased instability of the EEG with bursts of synchronous slow activity. In uremic

coma, mitten waves or high voltage tri-phasic waves may resemble those seen in hepatic coma. These discharges are occasionally confused with the spike and wave discharges of petit mal. EEG changes in diabetics have been described by Fabrykant<sup>6</sup> in a series of severely labile diabetics. Eighty percent had abnormal EEG's. Fifty percent were said to have severely abnormal records. Some of these patients had clinical seizures and many had "pseudo-hypoglycemia" consisting of nausea, fatigue, weakness, irritability and temper tantrums not relieved by glucose. These patients did not have typical EEG changes of petit mal absences but were felt by Fabrykant to have a type of seizure disorder. He stated that 5 out of 7 of these patients became easier to control on anticonvulsants and insulin.

Status epilepticus in patients with major motor seizures can be life threatening and is accompanied by total loss of awareness of the surroundings and total amnesia for the event. Patients with petit mal status frequently do purposeful acts and can recall the events happening during the seizure as though it happened in a dream like sequence.

Plum and Posner in their classic monograph "Diagnosis of Stupor and Coma"<sup>7</sup> list multiple causes of the comatose state. Petit mal status is not listed although the postictal state is. This young

Continued on Page 185

# ERCP

## (Endoscopic Retrograde Cholangiopancreatography)

IRVING J. POLINER, M.D.\*

For many years filling the common duct, hepatic ducts and the pancreatic ducts with contrast material usually necessitated a laparotomy. In 1968,<sup>1</sup> the ampulla of Vater was first cannulated and dye injected into the pancreatic duct through an oral instrument. By 1970 Ogoshi, Tobita, and Hara<sup>2</sup> and Takagi, et al,<sup>3</sup> had developed a simple practical method of cannulating the hepatic and pancreatic systems through the fiberoptic duodenoscope. Over the past six years, this procedure has become widespread and has helped clarify many problems of obstructive jaundice and pancreatic disease.<sup>4</sup> Recently, the technique of percutaneous transhepatic

cholangiography (PTC) with the "skinny" needle has added another method for outlining the hepatic and common ducts.<sup>5</sup> While there are differing opinions as to which of these is better, endoscopic retrograde cholangiopancreatography (ERCP) has distinct advantages. ERCP allows biopsy of an eroding lesion of the ampulla of Vater. It can be performed when a bleeding and clotting disorder makes the PTC unwise. ERCP may be successful where the PTC is not. Recently, papillotomy and removal of common duct stones by endoscopic retrograde cannulation has become available.<sup>6</sup> Finally, it remains the only method for nonsurgical visualization of the pancreatic ducts.

For the past year, ERCP has been performed at the Mercy Hospital. Most large centers report

\*Chief of Medicine (Gastroenterology), Mercy Hospital, Portland, Maine 04101.



FIG. 1

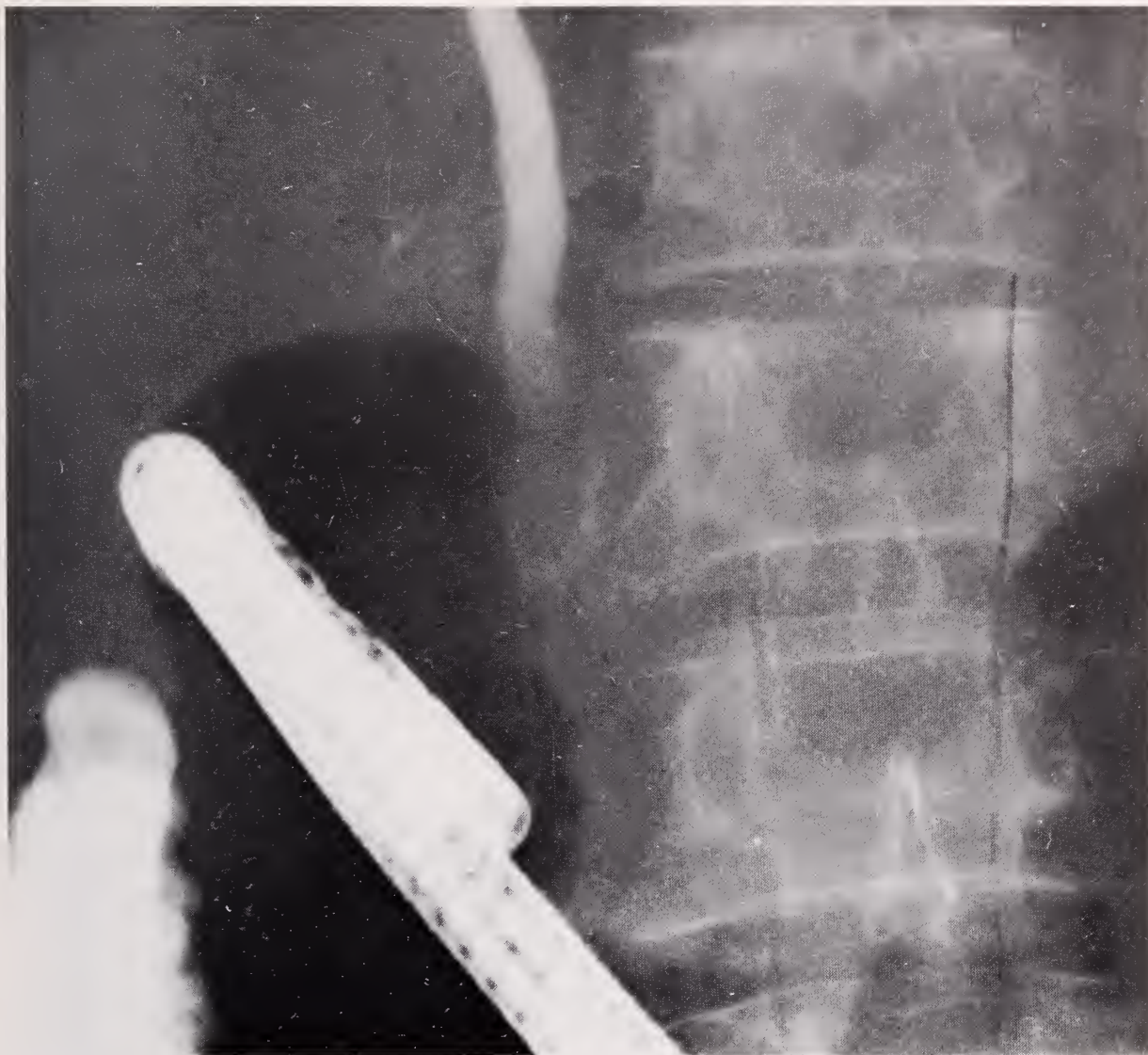


FIG. 2

75-80% success within 15-20 minutes.<sup>7</sup> Our most recent experiences have almost reached this goal.

Three representative cases where the ERCP has been helpful are discussed:

#### CASE #1

Mrs. R. C. is an 85-year-old white female who was admitted to the Mercy Hospital on September 16, 1976. For 3 weeks she had had increasing painless jaundice.

Physical examination showed an elderly, alert white female who was markedly jaundiced. The liver was 4 cm. down from the right costal margin; it was not nodular or tender. There were no palpable abdominal masses, and the spleen was not enlarged.

A CBC, urinalysis, amylase, prothrombin time, partial thromboplastin time were all normal.

A gastrointestinal series showed a small hiatal hernia and a Schatzki's ring. The duodenal sweep was normal. A liver scan was not diagnostic.

Liver function tests showed a bilirubin of 6.2 mg% with a direct fraction of 5.2 mg%. The alkaline phosphatase was 300 (normal to 85) and the SGOT was 150 units (normal to 55 units).

On September 23, 1976, an ERCP was performed. The catheter would not enter the common duct although it easily entered the pancreatic duct. Injection of dye outlined a dilated pancreatic

system with partial obstruction at the head of the pancreas. The following day a PTC showed complete obstruction of the common duct.

On September 30, 1977, a laparotomy showed a hard mass at the head of the pancreas obstructing the common duct and partially obstructing the pancreatic duct. A cholecystojejunostomy and jejunojejunostomy were performed. There was no tumor visible in the liver. She improved and was discharged to a nursing home.

#### CASE #2

Mrs. E. A. G. is a 71-year-old white female who developed anorexia, nausea, fatigue and jaundice in August 1976. In September 1976, she was evaluated at another hospital. Liver function tests were suggestive of hepatitis although the hepatitis antigen was negative. She was treated symptomatically. Her bilirubin remained elevated. The alkaline phosphatase rose to over 300 and remained at that level. She was referred for further evaluation.

She was hospitalized in January 1977. Physical examination disclosed a moderately jaundiced female. The liver was 12 cm. in over-all span; the edge was palpable at the right costal margin. The spleen was not palpable.

Laboratory data showed a prothrombin time of 43% which did not change with intramuscular aqua Mephyton. The bilirubin



FIG. 3

total was 3.8 mg% with a direct fraction of 2.8 mg%. Alkaline phosphatase was 280 (normal 10 to 85). SGOT was 320 units (normal up to 50 units). Antimitochondrial antibody titre and hepatitis B surface antigen were both negative. A Coomb's test was negative.

An intravenous cholangiogram showed no contrast material in the biliary system. The low prothrombin time made a liver biopsy or PTC unwise.

On January 26, 1977, an ERCP was performed. The common duct, right and left hepatic ducts, and the pancreatic duct were well filled and were all normal.

She was started on Prednisone 60 mg. per day and discharged from the hospital on February 24, 1977. Her bilirubin was 2 mg% (normal to 1.3 mg%), the alkaline phosphatase 84 (normal 24 to

71) and the SGOT was 27 units (normal 6-26 units).

### CASE #3

Mr. D. B. V. is a 29-year-old white male. In April 1975, he developed left upper abdomen, left anterior chest and left upper arm pain. In May 1975, he was evaluated at another hospital. His electrocardiograms, cardiac enzymes, and liver function tests were all normal. An oral cholecystogram and an upper gastrointestinal series were normal. No diagnosis was made.

He continued to have pain. In November 1975, he was seen by a cardiac consultant and a multilevel effort cardiogram was done. No evidence of cardiac disease was found. A diagnosis of "musculo-skeletal" pain was made.

He continued to be symptomatic. In January 1977, a repeat oral cholecystogram was normal. The possibility of pancreatic disease was considered, and he was referred for evaluation.

On February 9, 1977, an ERCP was performed at the Mercy Hospital as an outpatient procedure. Good visualization of a normal pancreatic duct was obtained. There were no symptoms following the procedure and he was discharged home one hour later. He was tactfully told that he had no organic disease. Psychiatric referral was suggested.

The indications, technique, results, and complications of ERCP has been well covered in the literature.<sup>4</sup> Our experience at the Mercy Hospital concurs with previous reports. The ERCP is a simple, safe, diagnostic procedure easily performed in a community hospital. In the future, removal of common duct gallstones by endoscopic papillotomy should become a community hospital procedure also.

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95 West Street, Portland, Maine 04102

### PETIT MAL STATUS EPILEPTICUS IN A PREGNANT ADULT

*Continued from Page 181*

diabetic patient in her fifth month of pregnancy demonstrates that the EEG can be extremely helpful when the more obvious causes of stupor or coma are eliminated. The electroencephalogram should always be included in the workup of a patient with prolonged confusion whether or not there is a clear history of seizure disorder preceding the onset of the confused state.

#### ADDENDUM

The patient was recently readmitted to hospital in petit mal status. She was in the seventh month of her second pregnancy and had not been taking medication fearing birth defects in her unborn child.

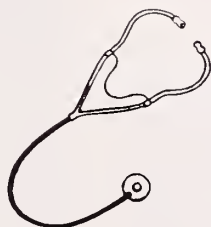
#### ACKNOWLEDGMENT

We wish to thank Dr. Elton R. Blaisdell for allowing us to study his patient.

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# Insulin Constant Infusion in a Community Hospital

PAUL S. BONJOUR, M.D.\*

Ketoacidosis and acute severe hyperglycemia remain important causes of morbidity and mortality in diabetes mellitus despite the availability of insulin for more than 50 years.

Many different regimens of insulin administration have been advocated in the management of diabetic ketoacidosis, but none generally accepted. Some authors have stressed the importance of ketonemia in deciding the initial dose of insulin, while others are guided by the initial blood glucose. In the presence of severe ketonemia, amounts of 300-400 I.U. of insulin have been advocated (Bradly 1971, Alberta 1972). Most regimens include complex advice about further doses to be given every 2-4 hours depending on the blood glucose response to the initial bolus. *There is a common impression that the more severe the acidosis, the more insulin is required.* Recent work has cast doubt on this.

Resistance to insulin action is said to exist in severe ketoacidosis and hyperglycemia as a result of inhibition of glucose utilization by ketones (Williamson and Krebs 1961) and as a result of antibody binding of insulin (Yalow 1961). For these supposed physiologic reasons, the large doses method, usually half subcutaneously and half intravenously, has been given to achieve total doses in the range of 300-500 IU per 24 hours. The rationale for giving intravenous insulin is that sub Q insulin may be poorly absorbed in the presence of dehydrating acidosis, and impaired peripheral perfusion.

FIG. 1

## RISK OF LARGE BOLUS INSULIN

1. HYPOKALEMIA
2. HYPOGLYCEMIA
3. HYPERLACTATEMIA

In one prospective study, as early as 1954, no difference in clinical response was found between groups initially receiving 80, 160, or 240 IU of insulin. And to date, no valid evidence that large doses of insulin are required, has been demonstrated. In fact, large doses may carry added risks, in particular hypokalemia, hypoglycemia, and hyperlactacidemia (Alberti 1973). Over the last 50 years,

occasional reports have appeared on the use of small doses of insulin (Fober and Host, 1927; Katsh, 1946; Jutzi, 1970). Recent articles by Generth 1973, Alberti 1974, and Kidson 1974, have reexamined this use.

FIG. 2  
INSULIN

MOLECULAR WEIGHT — 6000	
½ LIFE	3-5 MINUTES
ANTIGENIC	
FASTING SERUM	(I MG/L)

Insulin is a low molecular weight protein (about 6000) formed in the islets of Langerhans. Its biological half-life is 3-5 minutes.

FIG. 3  
INSULIN BINDING TISSUES

1. LIVER
  2. MUSCLE
  3. KIDNEY
- NOT BRAIN

It is bound to tissues on which it acts, mainly liver, muscle and kidney but not brain. It is antigenic and can be assayed, but antibody formation usually

FIG. 4  
TISSUE NOT REQUIRING INSULIN  
FOR ENTRY

1. BOWEL MUCOSA
2. RENAL TUBAL
3. BRAIN (EXCEPT HYPOTHALAMUS)

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takes a long time. In fasting serum, the normal concentration is 1 mg/liter. The purpose of insulin is to promote the utilization and storage of glucose.

First it helps get glucose into cells. The tissues which do not require insulin for entry are bowel mucosa, renal tubal and the brain except for the hypothalamus which tells us we are hungry. The other exception is liver, where glucose enters freely, but insulin's presence is necessary to determine certain enzyme activities whereas G-6 pd activity is inhibited by insulin.

**FIG. 5**  
INSULIN ACTION

1. GLYCOGEN SYNTHESIS
2. INHIBITION G6 PD
3.  $\blacktriangle$  INSULIN  $\blacktriangledown$   $\blacktriangleleft$  CIRCULATING AMINO ACIDS
4.  $\blacktriangle$  INSULIN  $\blacktriangledown$   $\blacktriangleleft$  PROTEIN SYNTHESIS
5. PUSHES K<sup>+</sup> INTO CELLS
6. ENTRY OF GLUCOSE INTO CELLS

Increase in circulatory insulin also leads to a fall in amino acid concentration, increasing protein synthesis, and insulin also figuratively pushes K<sup>+</sup> into cells.

The major stimulus to insulin surge is blood glucose above 100 mg%. It has been found that glucose by mouth leads to a greater insulin release than intravenous glucose because of release duodenal hormones such as glucagon.

The technique of constant IV infusion offers advantages over intermittent dose regimens. The insulin action begins at once and a steady blood concentration in the effective range can be maintained or terminated almost immediately. Because of the short intravenous half-life, the risk of hypoglycemia is negligible once the infusion is stopped. There has also been a reported marked decrease in insulin induced hypokalemia and its complications.

All patients with hyperglycemia need baseline glucose, electrolytes, BUN, and serum ph. The treatment is then begun. In the early days of its popularity, low dose meant about 30-40 IU insulin per hour by constant infusion. This was predicated by the fact that insulin is absorbed to the protein binding sites of glassware and IV tubing. To contract this, small doses of albumin were added to the bottle. Trials without this additive which carries a hepatitis risk showed the same rate of decline in blood glucose and clearing of ketoacidosis. This observation led to using even smaller per hour doses

**FIG. 6**  
BASE LINE LAB

GLUCOSE  
  
LYTES  
  
BUN  
  
SERUM PH

of insulin until our present 2-7 u/hr range was reached. Alberti's group gave all patients IV normal saline, and 6 IU/hr. This was continued until plasma glucose was between 160-250 mg%, when the normal saline was switched for glucose containing solution. In patients, whose initial electrolytes showed hypernatremia (Na>155), the solution was switched to 0.45 NS at first. Potassium supplements were added, only after urine output was documented and the initial K<sup>+</sup> was known.

**FIG. 7**  
AVERAGE K<sup>+</sup> REQUIREMENT

54 MEQ      AT      6 HOURS  
  
89 MEQ      AT      12 HOURS

Most patients required a mean of 54 meq<sup>K</sup> by 6 hours and 89 meq<sup>K</sup> by 12 hours. Less than one-half of the patients required bicarbonate (the indications vary author to author, but usually a ph less than 7.10). Of special note is that any patient who is hypo or normal kalemic on admission is in particular need of close observation and K<sup>+</sup> replacement. This is because the acidosis at the onset of therapy has resulted in exchange of H<sup>+</sup> ions into cells and K<sup>+</sup> out. With the correction of this acidosis, the K<sup>+</sup> reenters the cells revealing the true severe hypokalemia.

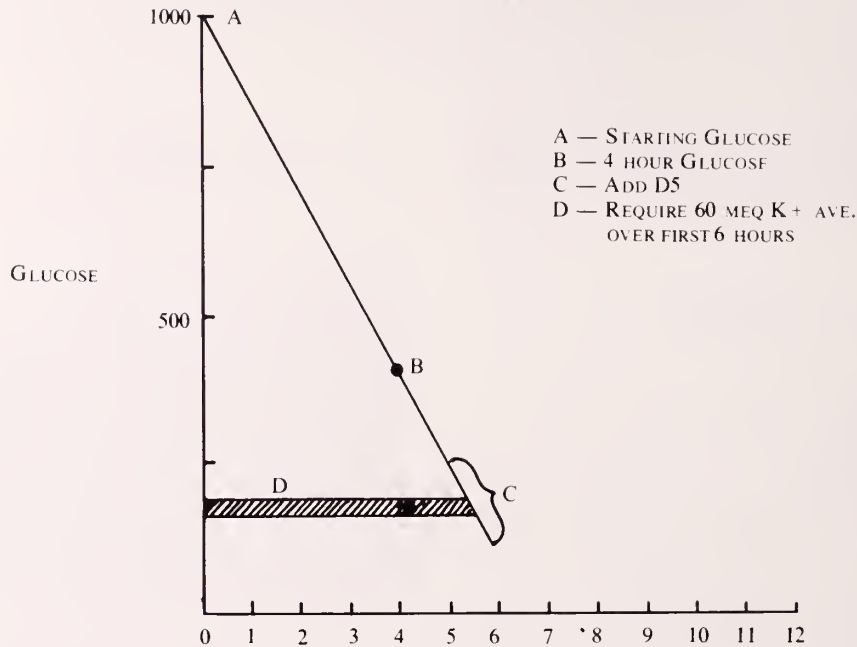
## DISCUSSION

In a 70 Kg patient, an infusion of 6 IU/hr produces an average steady state serum insulin concentration of 100  $\mu$ U/ml. In children, a dose of 0.1 IU/kg/hr is sufficient to achieve this concentration. In normal individuals, maximal hypoglycemia activity is achieved by insulin concentrations in the 20-200  $\mu$ U/Ml range. In 1972, Sonken demonstrated that the rate of fall of blood glucose in uncontrolled diabetics is uniformly rapid in this range and that these concentrations can be achieved by insulin infusions at rates of 2-12 IU/hr.

Studies have shown an average fall in blood glucose of 58% in 4 hrs. with this regimen — no differ-

**FIG. 8**  
RATE OF GLUCOSE FALL

SLOPE = 58%



ent than if 50 u/hr is used. The advantage of this method and its simplicity make it specially adaptable for the community hospital with its limited resources.

We use 60 U Reg. insulin per liter if normal saline, delivered by microdrip at 100 cc/hr, or by Ivac pump. Solusets can be added above for more control. A second vein is used for additional saline delivery initially. The dose is the same for all adults. For those not as far out of control and of smaller stature, lower doses from 2-4 u/hr are acceptable.

The second advantage is that it limits the need for a laboratory. After the initial stat blood work, you know that at the end of 4 hours your glucose will be about 60% of starting, and can be followed by hourly

Foley urines. The potassium can be followed less frequently due to the scarcity of hypokalemia with constant infusion.

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#### Scoliosis Clinic

A Scoliosis Clinic at Eastern Maine Medical Center has been established to provide evaluation and treatment for adolescents and children with spinal curvatures. It is designed to provide a team-multidisciplinary approach using the services of an Orthopedic Surgeon (Bob Gause, M.D.), a Physical Therapist (Ellen VanVranken, R.P.T.), and an Orthotist (Mark C. Picurro, C.P.O.), trained together in dealing with the many facets of scoliosis.

The Clinic is held every Wednesday afternoon in the Orthopedic area at Eastern Maine Medical Center. Appointments may be scheduled through Dianne Couture at 945-3496 or 947-3711 ext. 382.

# Utilization Review Chairman Speaks to the Staff\*

THOMAS F. CONNEEN, M.D., M.A.\*\*

I appear here to bring a message, and to initiate a plea for cooperation with Utilization Review. I am here to give you, as briefly as possible, an update on Utilization Review, a panoramic view, so to speak, of where it all began, where it is now, and where it is going.

I would like to start with a brief history of Utilization Review. Prior to 1965, there was no Utilization Review at the Mercy Hospital. No surgical or medical audit committees were in existence. It wasn't until the institution of Medicare that Utilization Review was undertaken. At that time, it was required that patients be certified on the 12th, 18th, and 30th day, by a member of the Utilization Review Committee. The Utilization Review process was reviewed by the State of Maine Department of Human Services, as well as by Blue Cross, the fiscal intermediary for Medicare in hospitals. As time went on, it seemed that this system was not effective. It did not encourage quality care at the least possible cost. Therefore, a new system of Utilization Review was started.

In the beginning, it was thought that pre-admission screening would be an effective process, however, this concept was challenged and dropped. In 1972, the President of the United States signed Public Law 92-603, The Social Security Amendments of 1972. Section 249F, Title II provides the steps for the basis of the formation of Professional Standard Review Organizations in the United States.

Although many portions of the provisions of this law were controversial and hotly debated, the House of Delegates of the Maine Medical Association in June of 1973, did adopt qualified compliance with the Statute. Qualifications included the provisions that the Statute should allow freedom of choice between the patient and physician, freedom of choice by the physician of the mode of therapy, and ability to maintain confidentiality of the record of any patient's illness, and liberal consideration for the welfare of the patients. Understood, but not mentioned under the stipulations by doctors of the Maine Medical Association for compliance with Peer Standard Review, was that great weight should be given to the judgment of the attending physician

regarding medical necessity of continued hospital stay.

The Pine Tree Organization for Professional Standards Review was incorporated on May 8, 1974. In July 1975, PTO was granted conditional status, and became the responsible review organization for Maine. The Pine Tree Organization is a part of the national group of professional standard review organizations that represents physicians', hospitals', and patients' interests at a national level. Many times the success in the political arena is measured not in terms of what happened, but in terms of what didn't — at least some degree of government control and intervention has to date been avoided.

The reason for the existence of Peer Standard Review Organizations is to maintain a standard, organized system of accountability. It seems that big business felt the cost of care was on the rise, that there was an inappropriate use of health care facilities, and the Federal Government and the fiscal intermediaries wanted accountability for the money spent. Actually, what they wanted was quality care at the least possible cost; quality care being defined as providing the patient with the greatest achievable health care benefits, with the minimal necessary risk, and the use of resources in the manner suitable to the patient. This definition seems to be widely accepted.

The purpose of Utilization Review, is assurance and accountability of the need for medical care in an acute hospital, and to satisfy three criteria:

1. Timely, appropriate and necessary admission to the acute hospital.
2. Concurrent review to determine the continued necessity of further stay in an acute hospital, as opposed to an intermediate care facility which is synonymous with the term nursing home; or ECF, or SNF, which is an extended care facility, or a skilled nursing facility respectively.
3. To assure that there was a high quality of care. This was to be achieved by concurrent review as well as retrospective medical care evaluation studies. In this regard, we are required at Mercy Hospital to do 4 medical care evaluation studies a year. Special retrospective studies, for the evaluation of medical care, may be requested.

Stated in another way, the object of Utilization Review, is to prevent if possible, unnecessary admissions to hospital for diagnostic work-up which could be done on an out-patient basis; to disallow benefits for cosmetic and dental surgery, unless there is a medical reason; to see that the patient is

\*Presented to the Medical Staff, Mercy Hospital, September 1976 and is solely the opinion of the author.

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discharged efficiently, effectively and timely to the appropriate level of care. Simply stated, for a patient to remain in an acute hospital, the patient should require daily, or more frequent visitation by the physician, and require the immediate availability of skilled nursing personnel.

As of June 1976, there were 15 PTO delegated hospitals. At this time, only 3 hospitals have requested non-delegations to all or part of the review. Total physician Pine Tree Organization Peer Standard Review membership in Maine is 942; in Cumberland County 244 M.D.'s; 56 D.O.'s.

In a community hospital, no matter how valid, or how constructive judgments may be, regarding a particular case or physician, this type of review often reaps unhappiness. However, it seems to be a necessary evil. The Pine Tree Organization's philosophy from the beginning has been that the responsibility for the review of medical care belongs with the practicing physician, in the context of his local hospital medical staff. This program allows Utilization to be undertaken by means of a process called 'Hospital Delegation', and this has been encouraged by the Pine Tree Organization. They have encouraged hospital staffs to accept this responsibility. It is designed to be the physician's program, in an attempt to prove that physicians will provide quality care at the least possible cost.

Utilization Review and quality assurance, is a process of understanding growth, and acceptance by all parties concerned, to achieve a common goal. As Medical Advisor I must consider several things: the hospital, the patient, the physician, and the fiscal intermediary; and know their needs and the obligations at all times. If we cannot show that we are capable of quality of care at a reasonable cost, we place in jeopardy, what I consider a rubber stamp for payment and we risk the outside intervention to the point of cookbook or computerized medicine — impersonal, inconsiderate, and dictatorial. In order to prevent further control and governmental intervention, it seems inevitable that there must be a sense of obligation, dedication, and an honest desire to comply with the memoranda of understanding with regard to health care deliverance at all levels.

Mercy Hospital was "Delegated" April 1, 1976 to do Utilization Review, medical care evaluation studies, and gather data on Title 18 — Medicare, Title 19 — Medicaid, and Title 5 — Maternal and Child Welfare Program cases. We have the rubber stamp, which means that if we adhere to, and fulfill the Memoranda of Understanding, there will be prompt payment of submitted bills of patients under these programs, and there will be no retrospective denial of payment. We become through delegation responsible via the U.R. process for the review within the hospital rather than have outside intervention which could be so objective and impersonal as to result in a great deal of unhappiness and loss of control regarding utilization of hospital facilities and services.

There are people who believe and hope that physicians cannot do Utilization Review, nor assure that admissions to the acute hospital are timely, appropriate and necessary. It is also felt by some that physicians cannot reduce the length of stay.

Physicians and the Pine Tree Organization are challenged to establish quality care by the developing norms and criteria, and by retrospective evaluation to identify problem areas — producing sub-standard care or prolonged hospitalization.

Since we became a hospital delegated to do our own review, we have had no retrospective denials of payment. All bills will be paid as long as we do what we are supposed to do as far as documentation, and are accountable to the Pine Tree Organization. I have seen a growing acceptance of the present process, which to me is the lesser of many evils. However, there is still a need for greater understanding, guidance, and direction to develop, and implement Peer Standards Review. For me, this has been an exciting new adventure, and I foresee that if we don't make it work, we will be controlled by non-professional bureaucrats and eventually come down to pre-admission screening. It seems imperative to assure accountability for the quality of care, necessity of care provided with the least possible cost, that PSRO and the Maine Pine Tree Organization is perhaps the last chance.

We all know that the delivery of health care has changed as has reimbursement. It is my opinion that the best utilization and the elimination of prolonged stays, unnecessary admissions, admissions for diagnostic workups, occurs when the patient pays his own bills. If patients were required to do this now, as they were years ago, they would demand to get out of the hospital when they realized it cost them \$85.00 to \$105.00 per day. Now things are different. If national health insurance comes in, it will be worse; the patient will have to pay even less. It is unrealistic to expect patients to try to pay their bills, with costs so high, and the idea of patients paying does not assure a high standard and quality of health care. If Government care, "cradle to the grave", payment for health care is enacted, a great deal more bureaucracy will be created and taxes will increase as will restraints.

We who are intimately involved must be able to work through the turmoil and conflicts to become more attuned to ever changing creative forces which are trying to shape the destiny of health care facilities. We must hope for wisdom, counsel, guidance, and direction, so that we do not continually meet with road blocks and detours. Hopefully, we will be able to establish a harmonious relationship with the Department of Human Services, Blue Cross-Blue Shield, Bureau of Quality Assurance, the Bureau of Health Insurance, PTO and fulfill our memorandum of understanding in an equitable fashion, implementing a system of quality care at a reasonable price, via a fair and realistic system of Utilization Review.

What, as physicians, must we do to fulfill the

Memoranda of Understanding with PTO-PSR? The following are suggestions. We must not admit patients only for consultations and diagnostic workups, which could be obtained on an out-patient basis. We must not do unnecessary studies. We must plan an orderly workup, and not a haphazard, piecemeal workup. In the past, I have seen workups done in 10 days which could have been done in four. We must not have patients waiting 4 to 5 days for surgery. If possible, discharge, and re-admit the day prior to surgery. The hospital is not a country club, rest home, custodial care facility, shelter, or day care center. We must not admit patients for our convenience, patients' family convenience, or for a vacation. We must try to place the patient at the appropriate level of care, when the patient can safely go to that level of care. Once the patient has reached the level of skilled nursing care, steps should be immediately taken for transfer without undue delay. Maximum advantage should be taken of the Social Service Departments and the Discharge Planners. Discharge transfer summaries should be completed, if possible, three days prior to anticipated discharge.

If we, as physicians, are aware of these musts, the rubber stamp will not go. If we are not cognizant of these musts, the Federal Government will scrap the so-called physicians' program of accountability. On the horizon is National Health Insurance. This will come if we show that we are incapable of achieving the goal expected of us, which is now a reasonable one, but tomorrow it may be unreasonable.

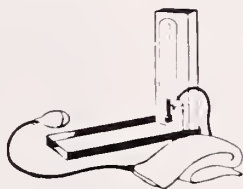
We have worked too hard to get where we are, only to let bureaucrats rule or shape our destiny, to the point of pre-admission screening, dictate whom we may treat and who may receive treatment, why, when, and where, and at what fee. At the present time, the rules are simple, and within peer control. Documentation is necessary, and I appeal to you for unified effort, cooperation, understanding and acceptance at the Mercy Hospital, to make the simple system work, and to document the necessity of continued stay in an acute hospital. Estimate the

number of days desired. State plans for discharge. In the early course of hospitalization, anticipate plans for discharge, and use the resources available, because it may take some patients 7 to 10 days to get into the nursing home of their choice, and that long, if welfare benefits have to be obtained before acceptance to the nursing home. Medicare will not pay for a patient that is in the acute hospital awaiting nursing home placement beyond 3 days after the decision is made that the patient has reached that level of care.

Since July of 1975, the Pine Tree Organization has been on a conditional status, and until such time that they are off this status, they are subject to review by Blue Cross, Medicare Dept., and the State Department of Human Services. We must assure that we are capable of Utilization Review, through the process of establishing standards, criteria, and norms, and through delegation of hospitals. In addition, at the present time, the Bureau of Quality Assurance, and the Bureau of Health Insurance, are looking over the shoulder of Pine Tree Organization. Representatives of Blue Cross Medicare Dept. are coming in to delegated hospitals on a quarterly basis, to assure that the delegated hospitals are fulfilling their requirements of Utilization Review, and that Pine Tree Organization is fulfilling its responsibility of seeing that the delegated hospitals do the job, and hence, it becomes, as I call it, a system of the police policing the police.

The Mercy Hospital has a memorandum of understanding with the Pine Tree Organization, and has been delegated the responsibility of assurance of quality care, timely efficient, effective and appropriate Utilization Review and discharge planning as well as a responsibility to incorporate the results of medical care evaluation studies, into continued staff education. This memorandum of understanding has been approved, and endorsed by the Executive Committee of the Medical Staff, Administration and you, as well as by the Board of Trustees.

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# Severe Protein-Calorie Malnutrition in a Hospital Setting†

W. EDWARD JORDAN, JR., M.D., F.A.C.S.\* and VIRGINIA E. JORDAN, Ph.D.\*\*

## INTRODUCTION

Malnutrition develops in hospitalized patients more frequently than is commonly recognized. Large numbers of patients may be marginally depleted, but only a few present a more severe picture.<sup>1</sup> Even here our recognition of the situation may be imperfect. The nutritional state of the patient after a long hospital stay depends upon the interaction of several variables. These include the nutritional state on admission, the intake of nutrients during hospitalization and the catabolic effects of the disease process.

## NUTRITIONAL STUDY

In order to obtain more information on the nutritional state of elderly hospitalized patients, a study of dietary history, anthropometric measurements, serum albumin, and the morphology and biochemical characteristics of hair roots was begun. The main attempt is to delineate borderline protein-calorie malnutrition. Hair root protein is thought to be a potentially important parameter. Considering homeostatic mechanisms, it would seem logical that if protein-calorie malnutrition existed, that available raw materials would be shunted away from such less vital protein synthetic activities as hair growth to more vital ones such as wound healing.<sup>2</sup> In conducting this work, suitable patients were selected from a general surgical practice. This report is on one of the subjects of this continuing study.

## CASE PRESENTATION

Mr. G. B. was admitted to the hospital on July 14 and discharged on September 26, 1975. When it was decided to include him in the study mentioned above, appropriate consent forms were obtained, a formal dietary history was taken, anthropometric measurements and serum albumin determinations were made and hair roots were extracted for analysis.

Mr. G. B. is an 84-year-old male.

**PROBLEM #1.** *Cerebrovascular accident, status post* — inactive.

**PROBLEM #2.** *Arteriosclerotic heart disease.* **SUBJECTIVE:** No shortness of breath — no cough. He is able to walk on the level with a below-the-knee prosthesis without difficulty. No

angina. **OBJECTIVE:** The lungs are clear. Extensive anasarca previously present is now absent. BUN-40. He takes Digoxin,<sup>®</sup> .25, and Lasix,<sup>®</sup> 20 mgs. daily. Electrolytes were normal. **ASSESSMENT:** The patient is compensated. **PLAN:** Continue medications. If cardiac failure does not recur and I.V. fluids are given slowly, he should tolerate surgery satisfactorily.

**PROBLEM #3.** *Diabetes mellitus.* **SUBJECTIVE:** Zero. **OBJECTIVE:** The blood sugars are in the 130-140 level. He has never taken insulin. **ASSESSMENT:** Maturity onset non-ketogenic diabetes. **PLAN:** Some insulin with I.V.'s — otherwise follow the blood sugar.

**PROBLEM #4.** *Hepatomegaly* — inactive. This was apparently a result of cardiac decompensation associated with Problem #2.

**PROBLEM #5.** *Below-the-knee amputation on the right.* **SUBJECTIVE:** Able to walk and tend his needs with the prosthesis and a cane. **OBJECTIVE:** Shows a well-healed, below-the-knee stump. **ASSESSMENT:** Good result from sympathectomy and below-the-knee amputation for gangrene 1 year ago after the vascular surgery service felt that reconstruction was not possible because of inadequate runoff. **PLAN:** Zero.

**PROBLEM #6.** *Gangrene of left foot.* **SUBJECTIVE:** Pain occurs in the foot both at rest and with activity. **OBJECTIVE:** Black discoloration of the fourth and fifth toes extending onto the dorsum of the foot. Temperature cool. Capillary filling markedly prolonged. The popliteal pulse is present. **ASSESSMENT:** This patient is faced with loss of limb. Ambulation will only be possible for him if the loss can be limited to a portion of the foot. **COURSE IN THE HOSPITAL:** Sympathectomy was performed and the extremity became warm. A transmetatarsal amputation was performed, but this failed; the foot became gangrenous and an above-the-knee amputation was performed. **PLAN:** Bed and wheelchair existence. Physiotherapy directed at arm strengthening to improve his capability of helping himself.

**PROBLEM #7.** *Protein-calorie malnutrition.* **SUBJECTIVE:** On admission to the hospital the patient felt vigorous. He gave a history of good dietary intake. He was in bed over a prolonged period of time and with the exception of three days following his sympathectomy and one day following his transmetatarsal amputation he took his 1500 calorie diabetic diet without difficulty. **OBJECTIVE:** Well developed male who appears to be adequately nourished, although thin. Weight on admission — 108 lbs. Serum albumin — 3.7. **ASSESSMENT:** Apparently, from the serum albumin, the dietary intake, the patient was adequately nourished on admission.

## NUTRITIONAL FINDINGS

Mr. G. B. was placed in the study on September 5th. Some of the data became immediately available. His hair samples showed no normally growing hairs, and only 38 percent growing but degenerative. This has been correlated with protein-calorie malnutrition.<sup>3</sup> His body weight was 91 lbs. His serum albumin was 2.1 grams. These findings, of course, indicated a severe degree of protein-calorie malnutrition<sup>4</sup> which had gone unrecognized on the ward. Daily weights had not been obtained and his serum albumin values had not been repeated. When these were done, it was recognized that his increased metabolism, associated with multiple operations, and a gangrenous foot had exceeded his food intake. Mr. G. B.'s dietary intake was increased to 3,000 calories a day, which incidentally he tolerated without placing him on insulin, and his final surgical procedure was delayed until his severe catabolism was, at least, partially reversed.

*Continued on Page 210*

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Also supported in part by Biomedical Institute, Skowhegan, Maine 04976.

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# The Preoperative Review\*

W. EDWARD JORDAN, JR., M.D.\*\*

Considering the amount of material and the time devoted to it, there is a remarkably small volume of literature on the medical record. Some books and articles have been published by Dr. Weed<sup>1</sup> and a few others have been generated by contact with his vastly improved system.<sup>2</sup> Outside of this, almost nothing exists.

For more than 10 years, I have been preparing a portion of the medical record which appears to be important to good surgical care. At first I did this in the old source-oriented manner before becoming a convert to Dr. Weed's problem-oriented system. Now it is done in a problem-oriented approach. However, the most important part is the concept itself.

During the hospitalization of the surgical patient, the recording of certain events is of great importance. The admission history and physical examination, the diagnostic laboratory and x-ray data, the operative note, and the day-by-day postoperative care are all meticulously recorded. The final summary is, of course, another important step. In this usual sequence of medical writing, one of the most important events has been left out completely as far as the formal record is concerned.

When all of the data is in, the diagnosis determined as best we can, and the decision for surgical intervention has been made, the day before surgery I write a note on the chart entitled, "The Preoperative Review." This review considers symptoms, the diagnostic findings, and the reasons that have been advanced for surgical intervention. In newer notes, it considers each problem in order. In short, this final summary written at the end of the medical care and diagnosis and the beginning of surgical care documents the reason for each decision and clarifies the thinking of the surgeon and other specialists aiding in the patient's care. It collects all of the data into a reasonably comprehensible whole.

The following are examples of notes taken from my charts; first in the source-oriented manner, and then in the problem-oriented manner.

## "Preoperative Review"

This 77-year-old woman has been in the hospital for two weeks with proven rectal carcinoma. The lesion is moderately advanced, and while apparently movable, may have metastasized, although this is uncertain.

"She has hypertension; she is now off drugs. She has aortic stenosis. She is digitalized and not in failure.

"Malnutrition has been a problem. She has lost a great deal of weight, but good dietary intake and IV protein solutions have been employed in the past week.

"Physical examination shows a few crackling rales at the lung bases. No neck vein distention. The heart is regular. The abdomen is soft and flat. No organ enlargement. No ankle edema. Rectal examination shows a large movable tumor.

"Chest x-ray shows a questionable infiltrate in the right upper lobe. This could be metastatic or could be an old acid-fast infection. No sputum could be obtained. I do not feel that surgery should be cancelled because of this. Blood is ready and the hemoglobin is 12 grams. The bowel prep. is completed, and abdomino-perineal is planned for tomorrow."

The second report which I would like to quote is written in the problem-oriented manner.

## "Preoperative Review"

### "Problem #1, Regional ileitis"

"*Subjective:* Right lower quadrant pain and abdominal distention occur. They are greatly reduced on clear liquids and Flexical, but when food is given, they rapidly reappear.

"*Objective:* There is one small exquisitely tender area above and to the right of the umbilicus. The patient had a resection and a by-pass procedure in the past 10 years. Total length of bowel removed or defunctionalized is small, as the procedures have been conservative. Colonoscopy to the transverse colon with visualization of the anastomosis showed no colonic involvement. Hemoglobin is 12.5 grams; blood is available. Bowel prep. is completed. The heart and lungs are normal.

"*Assessment:* I believe a narrow area exists above the anastomosis and this must be resected. If surgery is cancelled and food is given I believe that pain and distention will recur.

"*Plan:* Explore and resect tomorrow.

### "Problem #3, Hypoproteinemia.

"*Subjective:* The patient feels vigorous and strong, the best he has in several years.

"*Objective:* Has gained weight in the past six months. Serum albumin is 3.5 grams.

"*Assessment:* This has been a problem in the past, but is apparently inactive now. His reserves, however, must be low.

"*Plan:* Peripherally infused Dextrose and Freeamin postoperatively. I would use IV fat, but this is not currently available. Central venous catheterization and formal hyperalimentation will

*Continued on Page 217*

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## Antimicrobial Spectrum, Pharmacology, and Therapeutic Use of Antibiotics

### IV. Aminoglycosides

MICHAEL BARZA, M.D. and RICHARD T. SCHEIFE, Pharm.D.

The aminoglycoside antibiotics are amino sugars linked to another moiety by a glycoside bond.<sup>1</sup> Streptomycin was the first to be discovered (1944), and was followed by neomycin (1949), paromomycin (1956), kanamycin (1957), gentamicin (1963), tobramycin (1967), and amikacin (1972). Sisomicin and netilmicin are investigational compounds.

#### MECHANISM OF ACTION

This group of antibiotics, particularly streptomycin, has provided an invaluable tool for the study of protein synthesis in bacteria. The drugs accumulate within sensitive cells by a complex series of steps, one of which involves an aerobically-generated active transport system.<sup>2</sup> The antibiotics bind irreversibly to bacterial ribosomes, blocking the "recognition" step in protein synthesis and causing "misreading" of the genetic code.<sup>3,4</sup> The ribosomes separate from messenger RNA and cell death ensues.<sup>3</sup> Streptomycin-dependent mutants have been isolated; they possess a lethal ribosomal distortion which seems to be partially corrected by the superimposed distortion due to streptomycin.<sup>3</sup>

#### BACTERIAL RESISTANCE

Increasing resistance of meningococci, gonococci and enteric bacilli to streptomycin was recognized early,<sup>5</sup> and three general mechanisms for this phenomenon were defined: (1) alteration of the target (ribosome) so that its affinity for the antibiotic is lost; (2) reduced accumulation of the drugs within the bacterium; (3) elaboration of an enzyme which inactivates the antibiotic.

The first mechanism is primarily a laboratory phenomenon, although instances of selection of

such mutants have been reported in burn centers.<sup>4</sup> The second mechanism relates to the intracellular accumulation of antibiotic in sensitive cells: an important part of the transport process depends upon aerobically generated energy, and this may explain the resistance to aminoglycosides of bacteria growing under anaerobic conditions.<sup>2</sup>

Most of the resistance encountered clinically among aerobic bacteria is attributable to the formation of antibiotic-inactivating enzymes.<sup>4,6,7</sup> The genes controlling production of these enzymes are normally carried on extrachromosomal fragments of DNA called plasmids. Certain large plasmids are capable of transferring copies of themselves, by conjugation, into other bacteria. Such plasmids are called "R" factors, and frequently confer simultaneous resistance ("infectious drug resistance") to more than one antibiotic.<sup>8</sup>

Susceptibility of bacteria to the different aminoglycosides varies, depending upon the specificity of the inactivating enzymes, the degree of affinity of the antibiotic for the ribosomes, and possibly, the efficiency of the transport system for intracellular accumulation of the drug. Amikacin may constitute an exception to this general rule in that the majority of resistance reported to date appears to be due to problems of drug penetration into the bacterium: resistance to amikacin is usually accompanied by cross-resistance to the other aminoglycosides. The emergence of aminoglycoside-resistance during therapy is uncommon; when it occurs, it has been attributed to selection of a few colonies of resistant organisms by suboptimal therapy.<sup>9,10</sup> Unfortunately, the indiscriminate use of any one aminoglycoside seems to be capable of fostering resistance to other members of the class.

#### ANTIMICROBIAL SPECTRUM

Bacterial susceptibility to the aminoglycosides varies with geography and time. The data shown in Table 1, therefore, may not be fully representative of the situation in a particular hospital at a given moment. In most institutions at present, amikacin is active against a higher proportion of gram-negative aerobic bacilli (eg, 98%) than is gentamicin, tobramycin, or netilmicin (eg, 95%). Furthermore, the

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TABLE 1

ACTIVITY OF SYSTEMICALLY-ADMINISTERED AMINOGLYCOSIDES AGAINST COMMON BACTERIAL PATHOGENS<sup>a</sup>

Bacterium	Aminoglycosides (% inhibited)				
	Streptomycin	Kanamycin	Gentamicin	Tobramycin	Amikacin
<b>GRAM-NEGATIVE ENTERIC BACILLI</b> (aerobic)					
<i>E. coli</i>	50 <sup>11,21</sup>	80 <sup>12,13</sup>	95 <sup>13,14,22</sup>	95 <sup>13,14</sup>	98 <sup>12-14</sup>
<i>Klebsiella</i>	40 <sup>11,21</sup>	80 <sup>12,13</sup>	98 <sup>12-14</sup>	98 <sup>13,14</sup>	~100 <sup>12-14</sup>
<i>Enterobacter</i>	60 <sup>11</sup>	95 <sup>12,13</sup>	95 <sup>12-14</sup>	~100 <sup>13,14</sup>	~100 <sup>12,14</sup>
<i>Proteus mirabilis</i>	88 <sup>11</sup>	92 <sup>11-13</sup>	92 <sup>12-14</sup>	92 <sup>13,14</sup>	92 <sup>12-14</sup>
<i>Proteus vulgaris</i> , <i>morganii</i> , <i>rettgeri</i>	60 <sup>11,21</sup>	Generally 70 to 90%; as low as 30% for <i>P. rettgeri</i> <sup>11-14,16,22-24</sup>			
<i>Pseudomonas aeruginosa</i>	5 <sup>11</sup>	5 <sup>12,13</sup>	80-90 <sup>12-14</sup>	95 <sup>13,14</sup>	95 <sup>12-14</sup>
<i>Salmonella</i>	50 <sup>11</sup>	85-100 <sup>11,12,16</sup>	~100 <sup>11,12,16</sup>	~100 <sup>11,16</sup>	~100 <sup>12</sup>
<i>Shigella</i>	80 <sup>11</sup>	96 <sup>11,12</sup>	96 <sup>11,12</sup>	96 <sup>11</sup>	~100 <sup>12</sup>
<i>Serratia</i>	60 <sup>11</sup>	≥65 <sup>11-13</sup>	≥80 <sup>12-14</sup>	Variable <sup>13,14,23</sup>	98 <sup>12-14</sup>
<b>GRAM-POSITIVE COCCI</b>					
<i>Staphylococcus aureus</i>	80-95 <sup>5,11</sup>	98 <sup>12,13</sup>	~100 <sup>12-15</sup>	~100 <sup>13-15</sup>	100 <sup>12-15</sup>
<i>Staphylococcus epidermidis</i>	90 <sup>15</sup>	90 <sup>12,15</sup>	~100 <sup>12,15</sup>	~100 <sup>15</sup>	~100 <sup>15</sup>
Group A beta-hemolytic streptococcus	Weakly sensitive <sup>5</sup>	Weakly sensitive <sup>16</sup>	Weakly sensitive <sup>16-18</sup>	Weakly sensitive <sup>16-18</sup>	50% resistant <sup>12</sup>
<i>Pneumococcus</i>		Weakly susceptible <sup>5,19</sup>			
<i>Enterococcus</i>		Very few susceptible <sup>5,12,20</sup>			
<b>OTHER BACTERIA</b>					
<i>Haemophilus influenzae</i>			~100 <sup>25</sup>	~100 <sup>25</sup>	Moderately sensitive <sup>12</sup>
<i>Bacteroides fragilis</i>			-		
<i>Clostridia</i>		Not sensitive <sup>26,27</sup>			
Anaerobic cocci					

<sup>a</sup>Based on inhibition by the following concentrations, which are half of the usual therapeutic serum level: streptomycin 12 µg/ml;<sup>21</sup> kanamycin 12 µg/ml;<sup>21,22,28</sup> gentamicin 2 to 4 µg/ml;<sup>14,22</sup> tobramycin 2 to 4 µg/ml;<sup>14</sup> amikacin 10 µg/ml.<sup>22,28</sup>

majority of gentamicin-resistant strains are susceptible to amikacin, but the reverse is not true. These data underline the value of amikacin, but also caution against its indiscriminate use.

The activity of aminoglycosides is strongly affected by the physico-chemical milieu; for example, it is markedly decreased at pH 6.4, and variably altered at pH 8.4, conditions which might be encountered in urine and bile.<sup>14</sup> For purposes of Table 1, we have considered organisms susceptible if they are inhibited by levels of the drug which are one-half the usual peak serum concentration.

The aminoglycosides have found their greatest usefulness in the therapy of infections due to gram-negative aerobic bacilli. The majority of strains listed in Table 1 are susceptible to gentamicin, tobramycin and amikacin; a small percentage is resistant to kanamycin and a larger one to streptomycin. The comparative activity of the aminoglycosides is summarized in Table 2, with the principal emphasis on gram-negative aerobic bacilli.

*Staphylococcus aureus* and *epidermidis* are generally susceptible to parenterally-administered aminoglycosides. In contrast,  $\beta$ -hemolytic streptococci (group a), *Strep. viridans* and pneumococci

are weakly inhibited<sup>5,16-19,22,35</sup> and enterococci are generally resistant.<sup>5,20,22</sup> *Listeria* are readily inhibited by aminoglycosides.<sup>36</sup> Although gonococci and meningococci have not been examined extensively, the former were found to be fairly resistant to gentamicin in one study<sup>19</sup> and moderately sensitive in another.<sup>35</sup> (The aminocyclitol antibiotic spectinomycin which is used for therapy of gonorrhea is discussed later on.)

Anaerobic bacteria, including *Bacteroides fragilis*, clostridia and anaerobic cocci are generally not susceptible to aminoglycosides.<sup>26,27</sup>

Mycoplasma, including *Mycoplasma pneumoniae*, are inhibited by kanamycin, gentamicin and tobramycin.<sup>16</sup> *M. tuberculosis* is susceptible *in vitro* to streptomycin and gentamicin.<sup>25</sup>

#### COMBINATIONS WITH OTHER AGENTS

A synergistic (greater than additive) antimicrobial effect has been observed in a number of instances when aminoglycosides are combined with  $\beta$ -lactam antibiotics such as penicillins and cephalosporins (Table 3). The mechanism of this phenomenon, as studied in enterococci, is due to enhanced penetration of the bacterium by the aminoglycoside

TABLE 2

CLINICALLY IMPORTANT DIFFERENCES AMONG AMINOGLYCOSIDES IN THEIR ANTIBACTERIAL SPECTRUM		
Antibiotic	Spectrum	Comments
Streptomycin	Many gram-negative bacilli resistant.	The only aminoglycoside with demonstrated activity against <i>M. tuberculosis in vivo</i> . <sup>25</sup>
Kanamycin	Most pseudomonas resistant; some <i>E. coli</i> and <i>klebsiella</i> resistant.	
Gentamicin	Most aerobic gram-negative bacteria sensitive.	Resistance is still uncommon among gram-negative aerobes, but is increasing. Some strains of <i>proteus</i> , <i>klebsiella</i> , <i>serratia</i> , and <i>Pseudomonas aeruginosa</i> resistant.
Tobramycin	Similar to gentamicin. Bacteria highly resistant to gentamicin usually also resistant to tobramycin. <sup>29</sup>	Although most (90%) of strains of <i>Pseudomonas</i> are sensitive to tobramycin and gentamicin, tobramycin is inhibitory at 1/3 the concentration of gentamicin. <i>Serratia</i> may be less sensitive to tobramycin than to gentamicin. <sup>11,13,16,18</sup>
Amikacin	Similar to gentamicin, but active against many isolates of <i>proteus</i> , <i>pseudomonas</i> , resistant to gentamicin and tobramycin. <sup>30,31</sup>	A semisynthetic derivative of kanamycin which is resistant to many bacterial enzymes which degrade gentamicin and tobramycin. <sup>28,30</sup>
Netilmicin	Similar to gentamicin <sup>32-34</sup>	Considerable diversity exists in reports of various investigators comparing <i>in vitro</i> activity of netilmicin with other aminoglycosides. <sup>32-34</sup> Netilmicin is probably no more active than gentamicin against most <i>Enterobacteriaceae</i> ; organisms resistant to gentamicin will probably be resistant to netilmicin.
Neomycin	Activity lies between that of kanamycin and of gentamicin. <sup>35</sup>	
Sisomicin	Similar to tobramycin. <sup>14,16</sup>	

because of cell wall damage induced by the penicillin.<sup>46</sup> Synergism is not evident among enterococci which are extremely resistant to the aminoglycoside; such high level resistance is rare with gentamicin, but was found in 40% of strains with streptomycin, and 20% with kanamycin, when blood culture isolates in one hospital were studied.<sup>20</sup> A laboratory test is available to screen for extreme resistance to aminoglycoside antibiotics.

Carbenicillin and gentamicin are, as a rule, synergistic only against strains of *Pseudomonas* which are susceptible to the aminoglycoside (exhibit a zone of inhibition around a standard 10 µg disc).<sup>43</sup> *In vitro* synergism between carbenicillin or cephalosporins, on the one hand, and gentamicin or tobramycin, on the other, can be demonstrated for a majority of gram-negative bacilli aside from those shown in Table 3.<sup>45,47</sup> Moreover, there is a suggestion that the outcome of therapy of infections in immunosuppressed patients is better when the combination of drugs used is synergistic than when it is not.<sup>41,45</sup>

The other side of the coin, drug antagonism, has been demonstrated *in vitro* between aminoglycosides and clindamycin, chloramphenicol, or tetracycline.<sup>35,48</sup> However, contradictory data have also been reported.<sup>49</sup> Fortunately, in view of the frequency with which the combination is used, there is no evidence of antagonism *in vivo* between clindamycin and gentamicin.<sup>48</sup>

### PHARMACOLOGY

The aminoglycosides are highly polar molecules and are relatively insoluble in lipids. As a result: (1) they are minimally absorbed from the gut; (2) they penetrate the blood-brain and blood-ocular barriers

poorly; (3) their dosage is more accurately calculated on the basis of "lean" rather than total body weight;<sup>50,51</sup> (4) elimination occurs almost entirely by the kidney; and (5) they are moderately hemodialyzable. The pharmacokinetics of gentamicin, tobramycin, netilmicin and sisomicin appear to be very similar;<sup>52-58</sup> therefore, a common dosage schedule has been applied. Because of the similarity in the kinetics of kanamycin and amikacin,<sup>59-61</sup> these drugs are considered together, while streptomycin has been treated separately in this discussion. Detailed reviews of the pharmacokinetics of the aminoglycosides have been published recently.<sup>62-64</sup>

### Absorption

The antibiotics are well absorbed by intramuscular injection, producing peak serum levels after about one hour (30 to 90 minutes).<sup>52,61,62,65-68</sup> In contrast, less than 1% of an oral dose is absorbed, and the resultant serum levels are usually insignificant in individuals with normal renal function.<sup>63,65,67,69-72</sup> About the same amount of neomycin is absorbed whether given by mouth or by rectum, and uptake is not altered in the presence of ulcers or inflammatory bowel disease.<sup>72</sup> In contrast, gentamicin given orally is absorbed about five times as extensively in people with bacillary dysentery as in normals.<sup>73</sup>

Repeated oral or rectal dosing may result in the accumulation of toxic levels of antibiotic in patients with impaired renal function.<sup>70,74,75</sup> Intoxication may also occur when aminoglycosides are applied topically to large denuded areas such as wounds, burns and ulcers, or are used to irrigate joints. Occasionally, absorption from these sites may be so extensive as to cause oto- or nephrotoxicity in persons without antecedent renal impairment.<sup>65,73-74-78</sup>

TABLE 3

## SYNERGISM BETWEEN AMINOGLYCOSIDES AND VARIOUS ANTIBIOTICS

Disease	Synergism in Vitro	Synergism in Vivo	Comments
<i>Strep. viridans</i> endocarditis <sup>37</sup>	Penicillin G + streptomycin	No controlled trials	Many authors feel results not significantly different from penicillin G alone.
Enterococcal endocarditis <sup>20</sup>	Penicillin G or ampicillin + streptomycin or gentamicin	Yes <sup>20</sup>	Strains which are extremely resistant to the aminoglycoside do not show synergism.
<i>Staph. aureus</i> endocarditis	Nafcillin or oxacillin + aminoglycoside <sup>38</sup>	Not evident in preliminary studies <sup>39</sup>	Studies of this combination in humans are underway.
<i>Klebsiella pneumonia</i> or bacteremia	Cephalosporin + aminoglycoside <sup>40</sup>	Data suggestive, but not statistically significant <sup>41</sup>	Some authors have recommended such a combination, especially in the immunosuppressed host <sup>41a</sup> ; others rely upon a single antibiotic (cephalosporin or aminoglycoside) to which the organism is sensitive.
Serious <i>Pseudomonas</i> infections	Carbenicillin + gentamicin <sup>31,42,43</sup> tobramycin or amikacin <sup>31,40</sup>	Well demonstrated in experimental animals with or without granulocytopenia, <sup>42,44</sup> and clinical evidence exists of synergism in man <sup>41,45</sup>	For synergism to occur, the organism must be sensitive to the aminoglycoside. <sup>43</sup>
<i>Listeria monocytogenes</i> <sup>36</sup>	Penicillin G or ampicillin + streptomycin or gentamicin	Not studied	May be of value in patients with listeria meningitis or bacteremia with adverse prognostic factors.

TABLE 4

## SERUM HALF-LIFE AND DIALYZABILITY OF SYSTEMICALLY-ADMINISTERED AMINOGLYCOSIDES IN PATIENTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

Antibiotic	% Protein Bound	Half-Life (hours)		Renal Clearance (ml/min)	Dialysis Clearance (ml/min)	
		Normal Renal Function	Anephric		Hemodialysis	Peritoneal Dialysis
Gentamicin	0 <sup>55,63,84</sup>	249, <sup>54,65</sup>	30-60 <sup>54,62,63,79,86</sup>	73-85 <sup>54,63</sup>	26-48 <sup>54,86-88</sup>	5-10 <sup>79,89</sup>
Tobramycin	0 <sup>55,84,85</sup>	2-3 <sup>52,55,79,83,85</sup>	50-70 <sup>54,65,79,84,85</sup>	80-90 <sup>53,63,83</sup>	50-60 <sup>54,80</sup>	15 <sup>79</sup>
Kanamycin	0 <sup>55,67,84</sup>	2-3 <sup>60,61,65,68</sup>	40-80 <sup>62,65,74</sup>	70-80 <sup>61,67,68</sup>	30-40 <sup>86,90</sup>	5-8 <sup>65,79,90-92</sup>
Amikacin	0 <sup>60</sup>	2-3 <sup>59-61,66</sup>	30-86 <sup>59,92a</sup>	75 <sup>60,61</sup>	22 <sup>92a</sup>	6,4 <sup>92a</sup>
Streptomycin	30-35 <sup>62,65,84</sup>	2-3 <sup>62,65,84</sup>	100-110 <sup>62,63,65</sup>	30-70 <sup>65</sup>	1790, <sup>93</sup>	No data
Neomycin	?	3 <sup>62</sup>	?	?	30-50 <sup>74,90,94</sup>	10 <sup>90</sup>

## Peak Serum Levels

The aminoglycosides have similar volumes of distribution,<sup>60,61,65,68,79-81</sup> are eliminated by the kidney at comparable rates,<sup>60,61,65,67,68,82,83</sup> and are minimally protein-bound<sup>55,62,63,65,77,84,85</sup> (Table 4). Differences in their peak serum levels are chiefly a function of dosage; this is determined by a compromise between the therapeutic concentration and the level that can be achieved without substantial risk of toxicity (Table 5). Recently, fever has been shown to diminish peak serum levels of gentamicin,<sup>98</sup> but the clinical significance of this observation is unclear.

## Distribution

Because they are insoluble in lipids, the aminoglycosides are essentially excluded from most body cells including adipose tissue, and from organs such as the central nervous system and the eye. They are distributed in an extracellular fluid volume which constitutes about 30% of lean body weight<sup>51,81,99</sup>

(about 20 liters in an average adult); this fact can be used to predict the serum levels which will result from a particular dose; eg. 80 mg of gentamicin is distributed in 20 liters to yield a concentration of 4 µg/ml in serum and interstitial fluid.

Penetration of the blood-ocular barrier is so meager that effective therapy of bacterial endophthalmitis requires peri-ocular injections of the aminoglycosides.<sup>61,100-104</sup> Intrathecal or intraventricular administration is necessary to insure adequate concentrations in the cerebrospinal fluid.<sup>105,106</sup> In contrast, levels in synovial fluid and placental tissue are approximately 25 to 50% of those in the serum.<sup>62,65,69,107,108</sup>

The aminoglycoside antibiotics have a marked affinity for renal cortical tissue, accumulating in concentrations which are 10 to 50 times those in serum.<sup>67,107,109-111</sup> There are pronounced differences among the various agents in this regard, those which show the greatest tendency to accumulate being the most nephrotoxic.<sup>112</sup> Much lower levels of drug are

TABLE 5

## DOSAGE OF AMINOGLYCOSIDES IN ADULTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

Antibiotic	Desirable Serum Level ( $\mu\text{g/ml}$ )		Toxic Range ( $\mu\text{g/ml}$ ) <sup>b</sup>	Usual Dosage: Normal Renal Function (IM or IV)	Impaired Renal Function		Supplemental Dose After Each Hemodialysis <sup>c</sup>
	Peak	Trough			Initial (loading) Dose	Maintenance Dose	
Gentamicin							
Tobramycin	5-8	1-2	>10-12	1.7 mg/kg every 8 hours	2 mg/kg	0.8-1 mg/kg at intervals (hours) = 3-4 times the serum creatinine (mg/dl)	$\frac{1}{2}$ - $\frac{3}{4}$ of the loading dose
Sisomicin							
Netilmicin <sup>d</sup>							
Kanamycin	20-25	5-10	>30-35	5 mg/kg every 8 hours	7.5 mg/kg	3.5 mg/kg at intervals = 3-4 times the serum creatinine (mg/dl)	$\frac{1}{2}$ - $\frac{3}{4}$ of the loading dose
Amikacin							
Streptomycin	5-20	<5	>40-50	7.5 mg/kg (approx. 500 mg) every 12 hours	15 mg/kg (approx. 1 g)	See Appendix	Approx. $\frac{1}{4}$ of the loading dose

<sup>a</sup>Antibiotics within each group show similar pharmacokinetics (see text). In obese individuals, an attempt should be made to calculate all dosages on the basis of "lean" or "ideal" body weight rather than total weight.

<sup>b</sup>References: 62,63,65,73,81,85,87,95,96 for gentamicin, tobramycin, sisomicin; 63,69,97 for kanamycin, amikacin.

<sup>c</sup>The higher value should be used where some renal function persists, the lower one in individuals who are anuric.

<sup>d</sup>Toxic range and desirable serum levels not yet established; values are extrapolated from those for gentamicin and are probably underestimates.

found in the renal medulla. The tissue: serum gradients in both cortex and medulla may be strikingly diminished in diseased kidneys,<sup>101,109</sup> although not all authors agree on this point.<sup>110</sup>

### Elimination

The aminoglycosides are eliminated from the body by renal glomerular filtration. The half-lives are about two to three hours in patients with normal renal function, but are markedly longer in individuals with renal impairment (Table 4). Because the drugs are neither metabolized nor excreted in substantial quantities in the bile, hepatobiliary disease has little effect on their rates of elimination.<sup>62,65,67,107,110,113,114</sup> One exception is streptomycin, which displays a longer half-life in individuals with combined renal and hepatic disease than in those with renal disease alone.<sup>62</sup>

### DOSAGES IN PATIENTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

Selecting an optimal dosage of the aminoglycosides is difficult for two reasons. First, the toxic dose is not much greater than the therapeutic one (Table 5); second, there is considerable variation among individuals both in the peak level of drug produced by a given dose and in the half-life of the antibiotic.<sup>99,115</sup> Therefore, it is advisable to measure the peak and trough concentrations every few days, especially in patients with impaired renal function.

In order to saturate tissues and fluids with adequate concentrations of antibiotic, the initial (or "loading") dose for patients with serious infections should not be less than that shown in Table 5, irre-

spective of the state of renal function.<sup>51,116-118</sup> The aminoglycosides are only sparingly distributed into fatty tissue; hence, the dose in obese individuals should be based on an approximation of the "lean body mass" or "ideal body weight."<sup>50</sup>

### Dosage in Renal Impairment

A variety of approaches have been suggested for dosage adjustments in patients with renal impairment.<sup>64</sup> Many of these consist of equations or nomograms based upon the serum creatinine concentration or the creatinine clearance (Appendix). We have been unable to duplicate the high degree of predictability of serum concentrations claimed by the proponents of these methods, and prefer to rely upon the following simple rule-of-thumb guided by frequent measurements of the serum concentrations of antibiotic.

(a) *Half Dose Every Half-Life.* The serum half-life is the time required for the serum concentration of a substance to fall by 50%. If half of the loading dose is administered every half-life, serum levels will fluctuate between the peak and half of that concentration. For gentamicin, tobramycin, sisomicin and probably netilmicin,\* the "half-dose" is 0.8-1.0 mg/kg; for kanamycin and amikacin, it is 3.5 mg/kg (Table 5). It has been empirically observed that the half-life, in hours, can be estimated by multiplying the serum creatinine concentration (mg/dl) by 3 or 4.<sup>116,117,119</sup> The value 4 seems

\*There is accumulating, though still preliminary, evidence that netilmicin is less toxic than the other members of this group, and may be given in a somewhat higher dosage as shown in the footnote to Table 5.

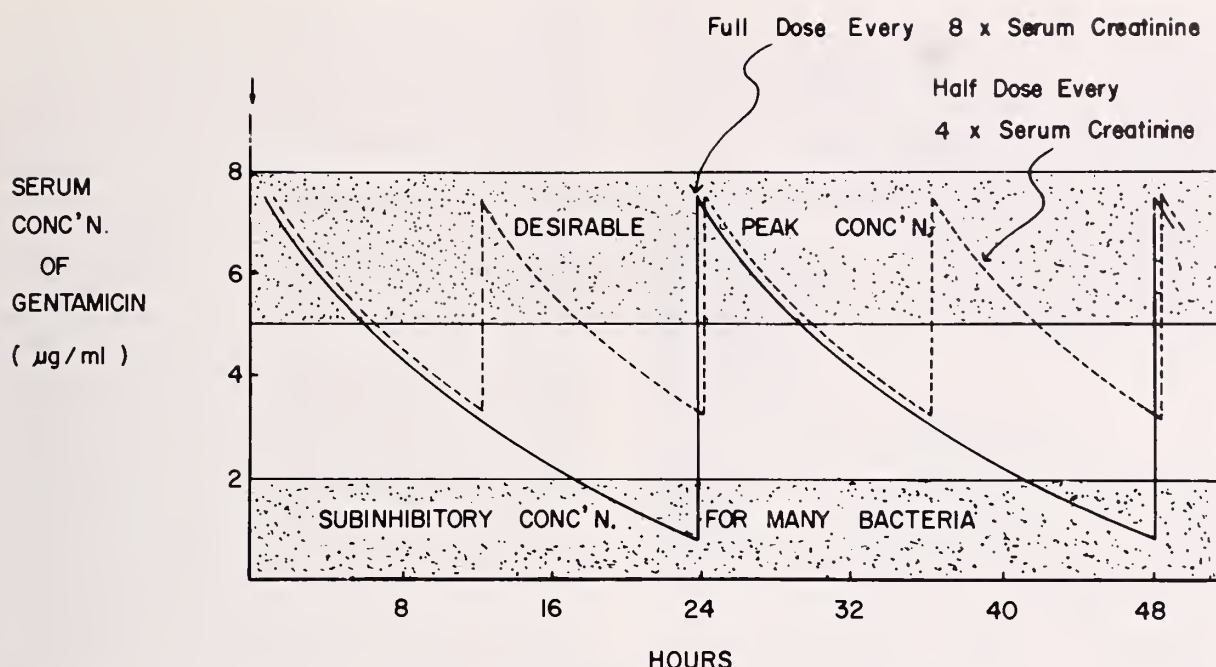


FIGURE 1

Comparative serum concentrations of gentamicin in the equilibrium state using two regimens: (a) half-dose every half-life, where half-life is taken to be approximately four times serum creatinine concentration (mg/dl) in hours; (b) full dose every two half-lives. Note that the latter method produces lower trough concentrations; although this may result in some reduction in aminoglycoside toxicity (not proven), there may be an increased risk of uncontrolled bacterial proliferation during these intervals of subinhibitory concentrations. Moreover, most workers have suggested that full doses be given every third rather than every second half-life in order to avoid drug accumulation (see text); this would prolong still further the period of subinhibitory serum concentrations.

to be more applicable to patients with serum creatinine concentrations of  $\geq 6$  mg/dl, and the value 3 for those with less severe renal impairment.<sup>117</sup> Thus, for a patient weighing 60 kg, with a serum creatinine concentration of 4 mg/dl, the dosage of gentamicin would be 48-60 mg every 12 hours.

(b) *Full Dose Every 2-3 Half-Lives*. In contrast to the first method, twice as much drug may be given half as often so that the total daily amount is the same. The dosages of gentamicin, tobramycin, sisomicin and netilmicin are 1.5-2.0 mg/kg, and of kanamycin and amikacin, 7.5 mg/kg; these are given at intervals, in hours, equal to eight times the serum creatinine (mg/dl).

As shown in Figure 1, the two methods produce similar peak levels of antibiotic, but trough levels are lower with the second approach. Although there is a suggestion that the incidence of toxicity is reduced by low trough levels,<sup>109,120,121</sup> this potential benefit of the second method appears to us to be outweighed by the risk that infection may be inadequately controlled during the intervals of low serum concentrations.<sup>64</sup> It should also be noted that after two and three half-lives, 75% and 87.5%, respectively, of the antibiotic is eliminated, rather than 100%; for this reason, many authors recommend somewhat less than a "full dose" every eight times the serum creatinine concentration, or that the interval be prolonged to 9-12 times the serum creatinine concentration (three full half-lives). The result is that serum levels of antibiotic are in the

therapeutic range for a lesser proportion of the day.<sup>64</sup> For these reasons, despite the absence of controlled comparisons, we prefer the first method, i.e. a half-dose every half-life.

It must be remembered that, in *elderly individuals*, a normal creatinine concentration often belies the presence of a minimal degree of age-related renal insufficiency.<sup>58</sup> Except in the most severe infections, it is best to err on the low side of dosage in such patients while awaiting the results of serum assays.

Whatever technique is used to adjust the dosage of aminoglycosides in patients with renal impairment, it is extremely valuable to measure the peak and valley concentrations every few days to insure that the patient is neither being underdosed nor overdosed. This is doubly important in individuals in whom the serum creatinine concentration is changing from day to day; for these patients dosage regimens based on a single creatinine concentration may be quite misleading and direct measurements of the serum level of antibiotic are almost indispensable. Blood for these determinations should be drawn just before, and approximately one hour after, the dose is given.

Carbenicillin has been shown to inactivate gentamicin *in vitro* and *in vivo*.<sup>122,123</sup> This interaction is of no clinical significance in individuals with normal renal function if the drugs are not mixed and allowed to stand before they are administered;<sup>124</sup> however, the half-life of gentamicin may be shortened consid-

erably in azotemic patients who are receiving carbenicillin.<sup>123</sup> Measurements of the serum level of antibiotic are particularly useful in this situation.

The aminoglycosides are minimally removed by peritoneal dialysis but are copiously hemodialyzable (Table 4). Thus, it is advisable to administer a supplemental dose after each hemodialysis. Because the extent of dialyzability may be profoundly affected by the type of coil used and the flow-rate through it, the supplemental dosages suggested in Table 5 must be regarded as rough estimates and should be modified according to the results of assays of serum concentrations of the drug.<sup>79,80,86-88,92-118</sup>

### ADVERSE REACTIONS

Allergic reactions, such as eosinophilia, rash, and fever, occur in approximately 1 to 3% of patients receiving aminoglycosides.<sup>62,65,125</sup> More serious consequences such as anaphylaxis,<sup>77</sup> agranulocytosis,<sup>126</sup> and other blood dyscrasias,<sup>65</sup> are extremely rare.

The most important adverse effects of this group of agents are "toxic" rather than allergic in nature, affecting the auditory-vestibular apparatus and the kidneys. The prevalence of these reactions can be correlated roughly with the length of treatment,<sup>62,127,128</sup> pre-existing renal impairment,<sup>62,125,128-130</sup> and the age of the patient.<sup>62,95,129</sup> The correlation with age may simply reflect the decrease in renal function commonly observed in elderly individuals.<sup>58</sup> It is not clear whether the toxicity is primarily related to an excessively high peak serum concentration, or to the absence of an adequate "trough" or "valley" level between doses.<sup>76,120,121,131,132</sup> There appears, however, to be a dosage range for each agent above which adverse reactions are relatively frequent (Table 5).

Although it is often stated that toxic effects are more likely to occur if the drugs are administered by rapid intravenous administration rather than by slow infusion, no evidence of this was found in one controlled study.<sup>133</sup> Nonetheless, rapid bolus injections of the aminoglycosides probably should be avoided.

### Ototoxicity

Two types of ototoxicity have been observed. Cochlear damage, manifested by varying degrees of hearing loss, especially for high tones, is characteristic of kanamycin, amikacin, neomycin and paromomycin. Vestibular impairment, resulting in disequilibrium, nystagmus, nausea, vomiting and vertigo, is more commonly associated with gentamicin, tobramycin and streptomycin. However, these distinctions are not absolute and any of the drugs can produce either or both forms of toxicity.

There is considerable disagreement as to the incidence of ototoxicity due to the aminoglycosides. In part, this may be due to differences in the accuracy of monitoring of dosages in earlier studies, and to variable attention to the detection of subclinical

damage by means of electronystagmography and audiometry. Overall, the incidence of *clinically-overt* ototoxicity in patients given usual dosages of antibiotics for not more than two weeks is approximately 2% for gentamicin<sup>62,65,73,77,129</sup> and 1% for kanamycin<sup>67,125,130</sup> and streptomycin.<sup>65,125,134</sup> Where less rigid criteria for dosage and duration of therapy were used, the incidence of this side effect has been found to be as high as 5 to 30% with kanamycin.<sup>65</sup> Although tobramycin appears to be less ototoxic than gentamicin in animals,<sup>53,96,135</sup> there is no basis for extending these impressions to humans. Preliminary data suggest that the incidence of eighth nerve damage with amikacin is similar to that with gentamicin.<sup>136</sup> The ototoxicity of netilmicin appears to be strikingly less than that of gentamicin in experimental animals;<sup>56</sup> however, controlled comparisons in man are not yet available. It must be emphasized that the frequency of subclinical ototoxicity is considerably higher than that of clinically-overt disease, approaching an incidence of 10-20% or higher with many of the congeners when these are given in high dosage for appreciable periods.<sup>97,136</sup>

There is also wide divergence of opinion as to the reversibility of aminoglycoside-related ototoxicity. Damage due to gentamicin appears to be reversible in about half the cases,<sup>129,131</sup> while that due to the other analogs may be less likely to improve with time.<sup>65,110,125,137</sup> Progressive eighth nerve damage after the drugs have been discontinued has been observed with many of the aminoglycosides with the possible exception of kanamycin.<sup>62,97,130,139</sup>

The ototoxic effects of the aminoglycosides are potentiated by coadministration of ethacrynic acid,<sup>62,65,138-140</sup> furosemide,<sup>62,139</sup> mannitol,<sup>138</sup> and possibly other diuretics.<sup>65</sup> Adverse effects are probably also increased by concomitant administration of other ototoxic antimicrobials, and perhaps by prior treatment with such agents.<sup>62</sup> It should be noted that vestibular dysfunction may be masked by the concurrent administration of drugs which suppress nausea and vomiting of vestibular origin and vertigo (eg, dimenhydrinate, meclizine).<sup>140</sup>

Recent investigations have shed light on the mechanism of ototoxicity. Aminoglycosides penetrate into the inner ear during periods of high serum concentrations and are slowly dissipated back into the bloodstream when serum levels are low.<sup>131,141</sup> The absence of sufficiently low trough levels (less than 2 µg of gentamicin per ml) for adequate periods each day may be an important determinant of ototoxicity.<sup>120,128,129,132</sup> Interestingly, the use of extremely sensitive measurements has demonstrated slight cochlear dysfunction during the administration of even a single dose of tobramycin; these changes occurred while serum levels were at their peak, though not in a range generally considered excessive.<sup>142</sup>

Patients receiving aminoglycosides should be observed carefully for signs and symptoms of ototoxicity; if possible, other drugs which may potentiate

this effect should be avoided. Although they provide only a rough guide, it is often helpful to monitor the serum levels of antibiotic. If long-term therapy (eg, more than 10 to 14 days) is anticipated, it may be useful to obtain sequential tests of auditory and vestibular function.

### *Nephrotoxicity*

Aminoglycosides damage the proximal tubular cells of the kidney, sparing the glomeruli. The resultant clinical picture is that of acute tubular necrosis of greater or lesser degree.<sup>74,143</sup> The mechanism of this phenomenon is not fully established; however, it is known that these antibiotics accumulate in renal cortical tissue in concentrations which greatly exceed those in the serum, and persist there for days following a single dose of drug.<sup>109,110,143</sup> Streptomycin, which is relatively free of nephrotoxicity, displays a much weaker affinity for renal tissue than do other aminoglycosides.<sup>112</sup> As is true of ototoxicity, the relative importance of the peak and trough serum levels is not clear.<sup>121</sup>

The incidence of clinically-significant renal damage varies widely among the congeners. As mentioned, streptomycin is essentially nontoxic in usual doses;<sup>74,77</sup> earlier reports suggesting a moderate incidence of renal dysfunction with streptomycin probably reflected the use of higher dosages and less pure preparations.<sup>74</sup> Gentamicin and tobramycin produce mild abnormalities of renal function in about 8% of recipients<sup>121</sup> and more severe effects in about 2%.<sup>62,73,77,85</sup> For kanamycin, and probably amikacin, the corresponding rates are approximately 6% and 3%, respectively.<sup>60,62,65,125,136</sup> Higher rates of nephrotoxicity have been reported with various aminoglycosides, especially in severely ill patients.<sup>144</sup> Data in animals suggest that netilmicin may be substantially less nephrotoxic than gentamicin, but controlled trials in humans are not available.<sup>56</sup>

Absorption of neomycin and paromomycin from mucosal surfaces can result in damage to the ear and kidney: this phenomenon is usually, but not exclusively,<sup>65,78</sup> seen in patients with pre-existing renal disease (see Absorption).<sup>62,72,74,75,137</sup>

In contrast to ototoxicity, renal damage is usually reversible if the aminoglycoside is discontinued at the first signs of renal dysfunction,<sup>67,73,74,77,121,130</sup> such as a rising BUN, serum creatinine, or the presence of protein or tubular cells in the urine.<sup>62,74,85</sup> Oliguria may or may not be present. One of the earliest signs of nephrotoxicity is the finding of lysosomal hydrolase enzymes in the urine:<sup>62,143,145</sup> however, most laboratories are not able to perform such determinations.

Considerable controversy exists over the role of other factors in promoting the nephrotoxicity of the aminoglycosides. There is general agreement that dehydration (and, by extension, potent diuretics),<sup>74</sup> methoxyfluorane,<sup>140</sup> the polymyxins, amphotericin B, and vancomycin<sup>74</sup> are capable of potentiating

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aminoglycoside-induced nephrotoxicity. Cephalothin was shown to have a similar effect in two studies,<sup>146,147</sup> but not in another.<sup>148</sup> A number of investigators have failed to show such an interaction between cephalosporins and aminoglycosides in laboratory animals; indeed, the former actually protected against aminoglycoside-induced nephrotoxicity when the two drugs were given simultaneously.<sup>149,150</sup> In the absence of more conclusive evidence, we continue to use cephalosporins with aminoglycosides in a variety of serious infections; for example, in the initial therapy of bacteremia of undefined etiology.

### *Neuromuscular Blockade*

The neuromuscular blockade induced by the aminoglycosides appears similar to that produced by conventional blocking agents, such as d-tubocurarine or pancuronium, and may result in weakness of skeletal muscles and respiratory depression. Patients with myasthenia gravis or severe hypocalcemia and individuals who have recently received other neuromuscular blocking agents appear to be particularly sensitive to this adverse effect.<sup>62,140,151,152</sup> Peritoneal lavage with solutions of these drugs may precipitate apnea,<sup>62,76,130</sup> possibly because high concentrations of the antibiotic come into direct contact with the diaphragm. Rarely, neuromuscular blockade has been observed following the administration of an aminoglycoside antibiotic by the intravenous or intramuscular route in the absence of any other predisposing factor.<sup>151,153</sup>

These antibiotics may impair neuromuscular transmission by a variety of mechanisms. They have been shown to inhibit the pre-synaptic release of acetylcholine and to depress the sensitivity of the motor endplate to acetylcholine.<sup>152,154</sup> In addition, the aminoglycosides may interfere with the action of calcium at the neuroreceptor.<sup>152,155</sup>

The propensity of the various congeners to block neuromuscular transmission differs widely; the relative potency being, in decreasing order: neomycin > streptomycin > kanamycin and amikacin > gentamicin and tobramycin.<sup>77,155,156</sup> Studies in animals suggest that netilmicin may be among the more active paralytics.<sup>56</sup> Blockade induced by any of the aminoglycosides can be partially or completely reversed by the administration of calcium salts intravenously.<sup>152,154,156</sup> The efficacy of cholinomimetic agents (edrophonium, neostigmine) is highly variable.

### *Malabsorption*

A reversible, dose-related malabsorption syndrome has been observed following the oral administration of neomycin, kanamycin, and paromomycin.<sup>62,65,71,157-161</sup> Two mechanisms have been implicated: (1) direct damage to villus cells, and (2) binding of bile salts and other micelle-dependent substances.<sup>65,157,161</sup> Impaired absorption of fat, protein, cholesterol, various sugars, iron,

digitalis, as well as other substances, have been noted. Indeed, neomycin has been employed in the treatment of hypercholesterolemia.<sup>65,157</sup> The ability of aminoglycosides to precipitate micelles appears to depend on their polybasic molecular structure and to be independent of their antimicrobial activity.<sup>157,160</sup> The effect is trivial or absent when the drugs are administered parenterally.<sup>65,161</sup>

### *Other Adverse Effects*

Certain other untoward reactions have occasionally been attributed to aminoglycosides, although the role of the antibiotic is often unclear. These include: (1) elevations of SGOT, SGPT and alkaline phosphatase;<sup>85</sup> (2) neurotoxicity manifested by pain and paresthesias,<sup>65,77</sup> blurring of vision, or an acute organic brain syndrome;<sup>130</sup> (3) optic neuritis (scotomas and enlargement of the blind spot);<sup>65,77,125</sup> and (4) depression of cardiac function following rapid parenteral administration of streptomycin or kanamycin.<sup>162</sup> Although the bowel flora is altered in patients receiving oral aminoglycosides, suprainfection is infrequent and acute enterocolitis is exceedingly rare.<sup>65,71</sup>

Streptomycin and kanamycin rarely can cause ototoxicity to the fetus; the safety of the other aminoglycosides during pregnancy is not established.<sup>163,164</sup>

## **THERAPEUTIC USE (TABLE 6)**

### *Gram-Negative Bacillary Infections*

The aminoglycosides are highly effective for infections due to a variety of aerobic gram-negative rods which are resistant to less toxic drugs (penicillins, cephalosporins). They are also valuable in combination with a penicillin, cephalosporin, and occasionally, chloramphenicol or clindamycin in the initial therapy of suspected bacteremia pending identification of the infecting organism. For empiric treatment of bacteremia in the immunosuppressed host, any pair of the following drugs provides equally effective therapy: a cephalosporin, carbenicillin (or ticarcillin), and an aminoglycoside.<sup>146,147</sup> It is useful to bear in mind some common pathogens which are not "covered" by frequently-used combinations (Table 7).

### *Combination Therapy for Defined Single Organisms*

There are many examples of *in vitro* synergism involving aminoglycosides; however, only a few of these have been examined and shown to be of value *in vivo* (Table 3). The best known example is *enterococcal endocarditis* for which penicillin G or ampicillin should be combined with streptomycin or gentamicin.

Streptomycin, but not gentamicin,<sup>25</sup> is a first-line *antituberculous* drug. It should always be given in combination with other agents to forestall the development of antimicrobial resistance.

*Pseudomonas bacteremia* remains a disease of

TABLE 6

THERAPEUTIC USE OF AMINOGLYCOSIDES<sup>b</sup>

Drugs of First Choice	Useful Alternative	Aminoglycosides "Cover"	Demonstrated Benefit in Combination	Ineffective or Weakly Effective
Infections due to aerobic gram-negative rods which are resistant to penicillins or cephalosporins (gentamicin or tobramycin)	Most gram-negative rod infections (gentamicin or tobramycin)	Mycoplasma	Enterococcal endocarditis (streptomycin or gentamicin)	Gonococcus, meningococcus
	Gonorrhea (spectinomycin only) <sup>a</sup>	Staphylococci		Anaerobic bacteria
		Salmonella	Tuberculosis (streptomycin)	CNS infection (unless administered intrathecally)
		Haemophilus influenzae		
Peritonitis (gentamicin or tobramycin)			Serious pseudomonas infection (carbenicillin with tobramycin or gentamicin)	Streptococci, pneumococci, enterococci
Non-gonococcal pelvic inflammatory disease (gentamicin or tobramycin)				
Most <i>serratia</i> (gentamicin, amikacin)				
Most <i>pseudomonas</i> (tobramycin, gentamicin or amikacin)				

<sup>a</sup>see text<sup>b</sup>Although we have suggested specific congeners in parentheses, the choice may be altered by the results of in vitro susceptibility data or the pattern of sensitivity in the particular institution.

TABLE 7

## COMMON PATHOGENS NOT INHIBITED BY SOME ANTIMICROBIAL COMBINATIONS\*

Combination	Organisms not inhibited	Comments
Cephalothin + gentamicin	<i>Bacteroides fragilis</i> Enterococci Some strains of <i>Proteus</i>	Neither drug penetrates CNS well
Carbenicillin + gentamicin		May not be as effective as clindamycin vs. <i>B. fragilis</i>
Cephalothin + carbenicillin	<i>Serratia</i> Some strains of <i>Klebsiella</i>	Resistant <i>pseudomonas</i> may emerge
Clindamycin + gentamicin	Gonococci, meningococci Enterococci	Neither drug penetrates CNS well
Penicillin G or ampicillin + gentamicin	<i>Bacteroides fragilis</i> Some strains of <i>Proteus</i>	
Chloramphenicol + gentamicin		May not provide optimal coverage for staphylococcus and enterococcus

\*In many instances (eg. carbenicillin for *Bacteroides fragilis*, gentamicin for *Staph. aureus*), the combination does not provide the best therapy for a given pathogen, but will generally suffice as a "holding action" until the specific organism has been identified.

high mortality despite the availability of potent anti-*Pseudomonas* antibiotics.<sup>165</sup> Because carbenicillin and aminoglycosides appear to exert a synergistic effect against this organism *in vivo*,<sup>41-43,44-45</sup> the combination should be strongly considered for the treatment of serious *Pseudomonas* infections, especially in immunosuppressed patients. In institutions with a substantial prevalence of gentamicin-resistant strains, amikacin will be the aminoglycoside of choice in this setting until the susceptibility of the infecting agent has been determined.

### Mixed Infections

Peritonitis and suppurative pelvic disease in women are generally due to a mixture of anaerobic and facultatively (optionally) aerobic organisms. These infections usually respond well to a combination of clindamycin and gentamicin; however, if there is any likelihood of the presence of the gonococcus, penicillin G should be included in the treatment. Penicillin G or ampicillin should also be added if there is persistent infection from which the enterococcus is cultured.

Aspiration pneumonia can generally be treated

with penicillin G alone. This generalization does not apply to patients who are at high risk of nasopharyngeal colonization by gram-negative enteric bacilli because of residence for several days or more in the hospital, endotracheal or nasogastric intubation, or exposure to broad-spectrum antibiotics; when aspiration occurs in this setting, it is prudent to add an aminoglycoside until the bacteriology is defined.

Although aminoglycosides are not drugs of choice, they will generally "cover" unsuspected *Mycoplasma pneumoniae*, *Staphylococcus aureus* and *epidermidis*, *Salmonella* and *H. influenzae* until more effective and safer therapy can be selected.

The aminoglycosides are *not effective* against anaerobic bacteria, meningococci, most strains of streptococci (including  $\beta$ -hemolytic streptococci and *Strep. viridans*), enterococci and pneumococci. Staphylococci are readily inhibited by aminoglycosides, but penicillins and cephalosporins provide much safer therapy for infections due to these organisms. Systemically-administered aminoglycosides do not penetrate the CNS well; therefore, treatment of meningitis with these agents generally requires intrathecal or intraventricular injection (see below).

*Spectinomycin*, which is actually an aminocyclitol rather than an aminoglycoside, is given in a single intramuscular dose of 2 g for the treatment of uncomplicated anogenital gonorrhea in patients who cannot receive, or have failed on, penicillin G with probenecid.<sup>166</sup> Repeated doses of spectinomycin may be effective for more extensive gonococcal infections. It also appears to be active against penicillin-resistant gonococci. The drug does not provide reliable therapy for syphilis. Although other aminoglycosides may be effective for gonorrhea when given in high dosage,<sup>166a</sup> they cannot be recommended for this purpose.

#### *Intrathecal and Intraventricular Gentamicin*

Gentamicin is useful in the therapy of meningitis due to aerobic enteric gram-negative rods.<sup>164</sup> Because of its poor penetration into the meninges even in the presence of inflammation, it should be given intrathecally for such infections.<sup>167-169</sup> A dosage of 4 mg produces peak cerebrospinal fluid concentrations of 20 to 40  $\mu\text{g/ml}$ ; this dosage should be repeated every 18 hours to maintain inhibitory concentrations.<sup>167</sup> The preferred vehicle is a relatively neutral solution such as normal saline without a bacteriostatic additive, or even cerebrospinal fluid itself. No adverse effects of the treatment have been observed with this regimen. For therapy of bacterial ventriculitis, it may be advisable to instill the drug into the ventricle through an Ommaya or Rickham reservoir because diffusion from the lumbar sac is inefficient.<sup>166</sup>

#### PROPHYLACTIC USE

Streptomycin or gentamicin in combination with

penicillin G is useful for the prophylaxis of endocarditis in patients with valvular heart disease who are undergoing abdominal or pelvic surgery. Topical, and occasionally systemic, gentamicin have been effective in the short run in preventing *Pseudomonas* infections in burn patients;<sup>170</sup> but this therapy should be discouraged because of the risks of fostering gentamicin resistance. Controlled studies have demonstrated the efficacy of oral neomycin together with erythromycin or tetracycline in reducing the rate of post-operative wound infections in patients undergoing bowel surgery.<sup>171</sup> Oral antibiotic mixtures have been thought to be of value in "sterilizing" the intestine of leukemic patients, thereby reducing the rate of infections.<sup>82</sup>

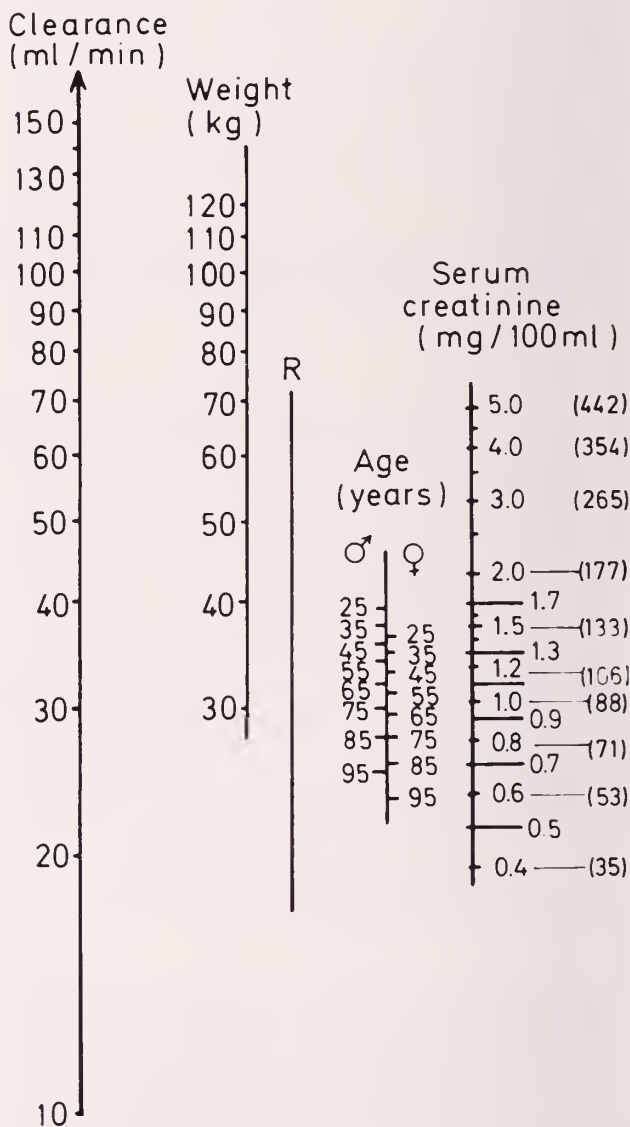


FIGURE 2  
Nomogram for Rapid Evaluation of  
Endogenous-Creatinine Clearance

With a ruler, join weight to age. Keep ruler at crossing point of line marked R. Then move the right-hand side of the ruler to the appropriate serum-creatinine value and read the patient's clearance from the left side of the nomogram.

(Reproduced with permission from Siersbaek-Nielsen.<sup>176</sup>)

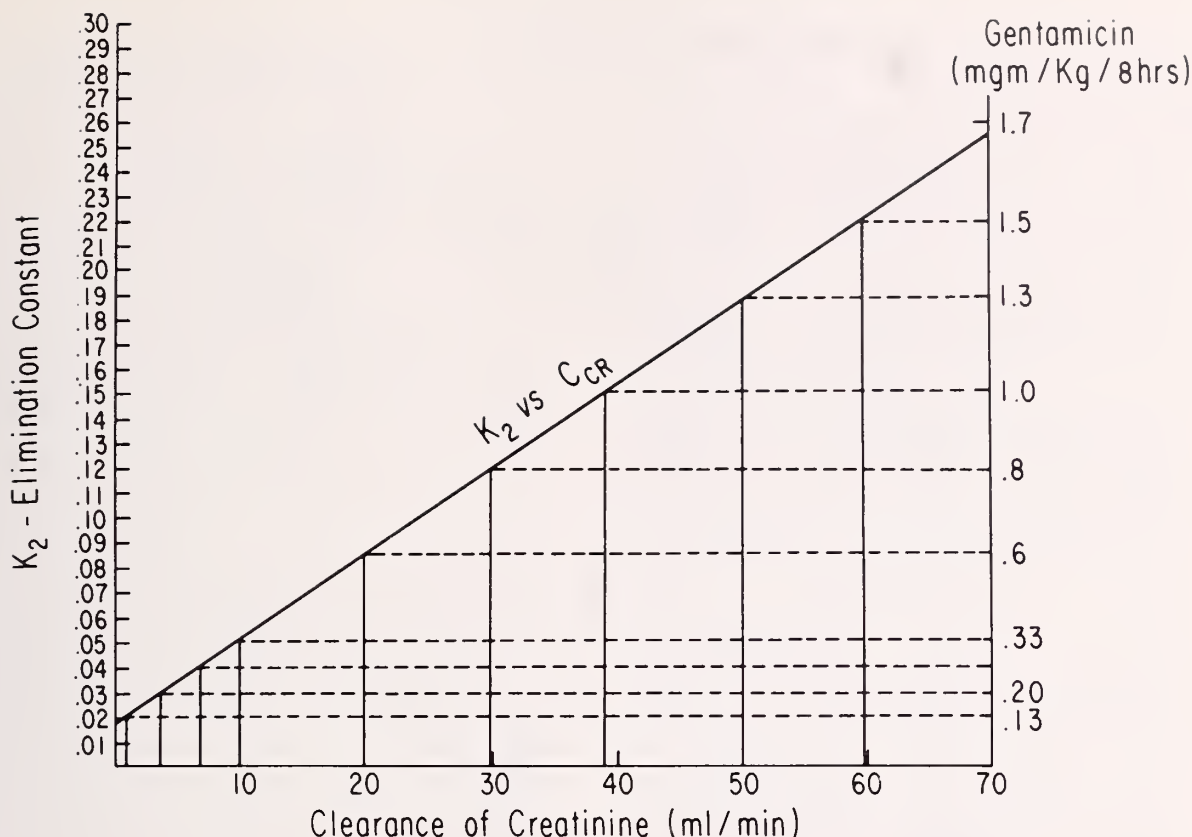


FIGURE 3

**Gentamicin, Tobramycin and Netilmicin Nomogram for Patients with Renal Failure**

To use the nomogram regimen, a loading dose of gentamicin, 1.7 mg/kg body weight, is administered. The sustaining dose is determined by passing a line perpendicular from the patient's  $C_{cr}$  value to the point where it intercepts the sloping line ( $K_2$  vs.  $C_{cr}$ ) on the nomogram. From the point of intercept, a horizontal line intersects the dose schedule, on the right side. This dose should be given every 8 hours for steady-state therapy.

(Reproduced with permission from Chan, et al.<sup>118</sup>)

Again, however, the risk of selecting resistant organisms poses a serious hazard.

**SELECTION OF AN AMINOGLYCOSIDE**

Clinical data support the value of *streptomycin* in the therapy of tuberculosis, brucellosis, tularemia, and yersinia infections; several of these require coadministration of another agent. The choice between streptomycin and gentamicin for combination therapy of enterococcal endocarditis may be simplified by knowledge of the prevalence of high-level streptomycin-resistant strains in the hospital, or by use of an *in vitro* screening test.<sup>20</sup> *Neomycin* is the agent used orally in the treatment of hepatic encephalopathy.<sup>172</sup> *Paromomycin* is presently indicated only for the treatment of amebic infections.

There appear to be no clinically-important differences among gentamicin, tobramycin and amikacin in their efficacy against infections due to susceptible organisms or in their relative safety.<sup>136,144</sup> Occasional organisms, chiefly *Pseudomonas* and *Serratia*, are sensitive to tobramycin but not to gentamicin, or vice versa; unfortunately, the fact that tobramycin is more active against *Pseudomonas* than gentamicin *in vitro* has not been translated into

improved clinical results.<sup>29,163</sup> The major difference among the drugs at present lies in the low but increasing prevalence of gram-negative bacilli which are resistant to gentamicin and tobramycin and susceptible to amikacin. As a result, in those institutions in which gentamicin-resistant strains are of concern, amikacin is the aminoglycoside of choice in high-risk patients (eg, those who are immunosuppressed, hospitalized for a prolonged period, or recently treated with an aminoglycoside antibiotic) until the antibiotic susceptibility of the infecting bacterium has been determined. If clinical experience — which is thus far limited — shows netilmicin to be effective and less toxic than other congeners, this drug may become the preferred agent for susceptible organisms.

**APPENDIX**

**NOMOGRAMS AND EQUATIONS FOR DOSAGE**

**ADJUSTMENTS IN RENAL FAILURE**

**(1) Clearance from Serum Creatinine Concentration**

The methods described in the body of this paper for adjusting the dosage of aminoglycosides in patients with renal failure (half-dose every half-life, or

# KANAMYCIN DOSAGE

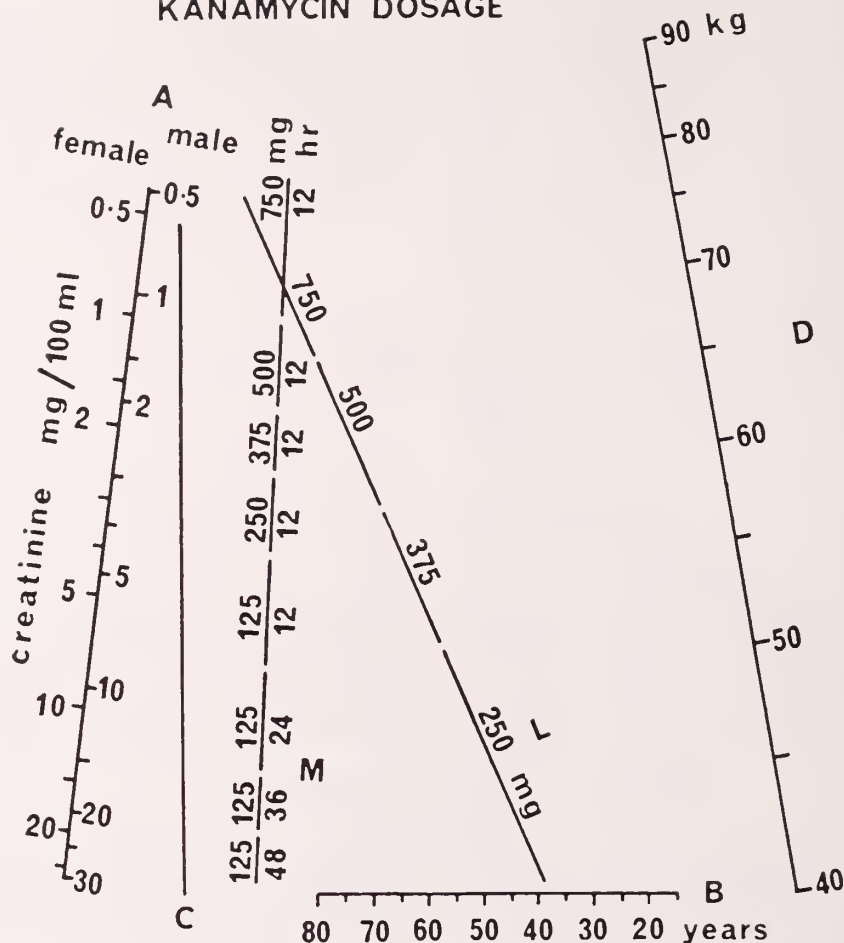


FIGURE 4

## Kanamycin and Amikacin Nomogram for Patients with Renal Failure

1. Join with a straight line the serum-creatinine concentration appropriate to the sex on scale A and the age on scale B. Mark the point at which the straight line cuts line C.
2. Join with a straight line the mark on line C and the body weight on scale D. Mark the points at which this line cuts the dosage lines L and M.
3. The loading dose (mg) is written against the marked part of line L. The maintenance dose (mg) and the appropriate interval (hours) between doses are written against the marked part of line M.
4. If the patient is severely oliguric, the dose schedule should be obtained by joining with a straight line the lowest point on line C to the body weight on scale D.
5. After a period of hemodialysis of 6 hours or more, a booster dose of half the loading dose is necessary in addition to the maintenance dose indicated by the nomogram.

(Reproduced with permission from Mawer, et al.<sup>177</sup>)

full dose every 2-3 half-lives) are relatively imprecise. To some extent, this reflects the inexactness of the serum creatinine concentration as a measure of the glomerular filtration rate, and hence, of the rate of elimination of aminoglycoside antibiotics. Although the creatinine clearance is a more reliable guide to the rate of glomerular filtration than the serum creatinine concentration, it is subject to errors in the accuracy of the urine collection, and is also an imperfect measure of the rate of glomerular filtration.<sup>173,174</sup> Many authors favor the use of an *estimated creatinine clearance*, which is based upon the serum creatinine concentration, and corrected for age, sex, and (in some instances) body weight. A formula and a nomogram for the deriva-

tion of creatinine clearance are provided for the calculation of the half-life of gentamicin and related drugs.

### (a) Formula<sup>174</sup>

$$\text{Males: Estimated creatinine clearance (ml/min)} = \frac{98 - [0.8 (\text{Age} - 20)]}{\text{Cr}_s}$$

$$\text{Females: Estimated creatinine clearance (ml/min)} = 0.9 \times \text{estimated creatinine clearance in males}$$

Age is expressed in years. Cr<sub>s</sub> is serum creatinine concentration (mg/dl)

### (b) Siersbaeck-Nielson nomogram:<sup>176</sup> see Figure 2

(2) *Gentamicin, Tobramycin, Netilmicin and Sisomicin in Renal Failure*

(a) Formula:<sup>51</sup>

$$t_{1/2} = \frac{3.5 \times \text{ideal body weight (kg)}}{\text{creatinine clearance (ml/min)}}$$

A dose of 0.8 - 1.0 mg/kg is given every half life

(b) Nomogram:<sup>118</sup> see Figure 3

(3) *Amikacin in Renal Failure*

(a) Nomogram:<sup>177</sup> see Figure 4

(4) *Streptomycin in Renal Failure*<sup>178</sup>

Normal renal function: 7.5 mg/kg every 12 hours  
Creatinine clearance 50-80 ml/min: 7.5 mg/kg every 24 hours

Creatinine clearance 10-50 ml/min: 7.5 mg/kg every 24-72 hours

Creatinine clearance < 10 ml/min: 7.5 mg/kg every 72-96 hours

In addition to these various regimens, it is possible to perform several sequential measurements of the serum levels of antibiotic after a dose and, by plotting the values on semilogarithmic coordinates, to determine the half-life of the drug directly. Despite the aura of precision and reliability that surrounds the various formulas and nomograms presented in this section, none of them has been shown to be substantially more accurate in the individual patient than the simple technique described in this paper (half-dose every half-life), and it is our belief that each of them should be monitored by assays of the peak and trough concentrations of antibiotic.

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## SEVERE PROTEIN-CALORIE MALNUTRITION IN A HOSPITAL SETTING

*Continued from Page 192*

### CONCLUSION

The development of severe protein-calorie malnutrition in this patient had been overlooked, and was discovered only when he was entered into an on-going study of nutrition in elderly hospitalized patients. It is important to be aware of, and measure, the nutritional state of our patients on admission and throughout their hospital stay.

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## BLUE SHIELD CHANGES MADE

The Blue Cross and Blue Shield Board of Directors approved changes for improvement in the Blue Shield line. Here are the changes summarized briefly:

(1) Starting June 15, 1977, U.C.R. rises in the ceiling will be tied to rises in fees for all other services in the economy. (All services - minus - medical care services component of CPI).

(2) Effective February 1, 1977, Blue Shield U.C.R. allowances are determined by using the State as a single area.

(3) As of March 1, 1977, the participating physician can consider Blue Alliance Major Medical as a payment source for balances of \$100 or more on Blue Shield covered services rendered to Subscribers who are eligible for Service Benefits.

(4) On July 1, 1977, we are expecting to market a new Schedule contract based on 1977 charges. The new "E" Schedule 1850 contract will feature:

- \* \$1850 maximum
- \* \$9,500 Service Benefit income level (family)
- \* Coverage of medically indicated lab work in office or certified lab
- \* Coverage of casting and surgical supplies for office surgery

(5) As of February 1, 1977, no further sales of the BSC-350 contract were being made (1979 phase-out planned).

(6) Also since February 1, 1977, we have been emphasizing UCR sales and the minimum group size for eligibility to purchase a UCR contract has been lowered.

(7) As of July 1, 1977, there will be an increase of benefit allowances in BSC and BSD contracts for: D & C, surgical assistant, and surgical removal of impacted teeth.

(8) Medically indicated lab work in office or commercial lab has been included in UCR based contracts sold after February 1, 1977.

(9) Studies during 1977 will be completed to determine feasibility for coverage of special diagnostic procedures and medical emergencies. A study will also be conducted annually for determination of need for additional levels of coverage.

Every physician was sent a letter, listing in detail the changes and rationales that prompted the change, along with the effective date of implementation.

# Necrology

DONALD L. ANDERSON, M.D.

1915-1977

Friends and colleagues in Lewiston and Auburn and across the State of Maine were saddened by the untimely death of Donald Leroy Anderson on March 26, 1977, after a brief illness.

Known widely as Bunny throughout his life in consequence of his birth on Easter day, April 4, 1915, he also acquired several other nicknames, a sign of the closeness of his friendships with people in all walks of life. His never-failing sense of humor was an outstanding personal trait which helped to lighten the day's burdens for many, particularly those with whom he had to work, thus endearing him to his assistants at all professional levels.

Bunny, the son of W. Leroy and G. Mildred Sawyer Anderson was born in Caribou and received his elementary and secondary education there. He graduated from the University of Maine in 1935 and received his M.D. degree from Boston University in 1940. Following internship at Eastern Maine Medical Center, he served in the U.S. Army Medical Corps from 1941 to 1945 and remained active in the Army Reserves with the 333rd General Hospital, locally. His overseas service career was distinguished by the receipt of two Bronze Stars and five Oak Leaf Cluster awards.

After completing his residency in Urology at the Massachusetts Memorial Hospital, Bunny joined the Medical Staff of the Central Maine Medical Center in 1948 and served as Chief of Urology for many years. At the time of his death, he was Vice President of the Medical Staff of this institution.

Dr. Anderson was active in County and State Medical organizations, serving for many years as the Secretary-Treasurer of the Androscoggin County Medical Society and as Delegate and Councillor to the Maine Medical Association. He was to have assumed the office of President of the Maine Medical Association

in June 1977.

In addition to his private medical practice, medical administrative responsibilities and numerous active consultative appointments, Bunny found time to participate actively in local Masonic organizations, including Kora Temple where he served on the medical staff. He was a parishioner of the High Street Congregational Church. He also was very interested in sports, both as advisor and physician to local high school teams and as an active and able participant. His interest and encouragement will certainly be long remembered by the many students he helped along the way.

Though Bunny obviously enjoyed the practice of medicine and everything connected with it, his greatest joy was in his family. He married Dorothy Sperling, M.D. in 1938 and their six children have been raised in an atmosphere of love and understanding which could well serve as an example to all young parents. Family activities occupied an important place in his life and the successes of his children are witness to his guidance and care.

It is appropriate that we, the Androscoggin County Medical Society, recognize the passing of Dr. Donald Leroy Anderson, friend, confidant and colleague and express to his wife Dorothy and his children Eric, Karl, Robert, Betsy, Margot and Carolyn and his mother, Mildred Stokes, our condolences in their loss and our heartfelt thanks to them for sharing with us their beloved husband, father and son.

## *Resolutions Committee*

JOHN W. CARRIER, M.D.

WALDO A. CLAPP, M.D.

LAWRENCE A. NADEAU, M.D.

## Letters to the Editor

To the Editor:

I share the same concern you do regarding the eventual switchover that Maine doctors will undergo in conforming with the recently enacted JUA (Joint Underwriting Association).

I feel sure that a large majority of the Maine Medical Association members will be asking — What is JUA? How will it affect me and what will be the cost?

JUA was created by Act of the Maine Legislature Chapter 444 of the public laws of 1975, to protect the availability of hospitals and doctors professional malpractice coverage in the event that the market for this professional liability coverage diminished or dried up. Since the time of its inception, the situation has worsened and last Fall, the Hospital segment of the bill was activated. For the past two years, companies providing Professional Liability Insurance for doctors were only renewing what they already had on the books, which meant that doctors coming into the state were unable to secure coverage, and had to resort to the Excess market with low limits of liability and high premiums.

Members of the JUA (Joint Underwriting Association) are companies authorized to write and to engage in writing personal injury liability insurance in Maine. Companies with assets totaling less than \$5,000,000 are not required to be members. The purpose of the JUA is to provide a temporary Market for medical Malpractice insurance on a self-supporting basis without subsidy from its members. The JUA is governed by a board of eleven members. Three directors are appointed by the Superintendent of Insurance of the State of Maine. Two of the appointed directors represent the Maine Medical Association and one represents the Maine Hospital Association.

The same act which created the JUA also created a Stabilization Reserve Fund administered separately by its own board of three directors. Its revenues come from a surcharge equal to 1/3 of the regular JUA premiums. All monies received by the Fund are held in trust by a bank selected by the Directors of the Fund. The Stabilization Reserve Fund is available to pay obligations of the JUA should premiums prove inadequate. If any money remains in the Fund, it will be returned to the policyholders.

Just recently, the Superintendent of Insurance sanctioned the JUA for Maine physicians which means, with the possible exception of two companies (St. Paul and Aetna), that when the policies now in force expire, doctors will have to apply to the JUA for coverage through the present producer. It will be possible to secure limits up to \$1,000,000/\$3,000,000, and the coverage will be on an "occurrence" basis. To avoid confusion and to insure continuous coverage, we can't caution any too strongly, that doctors prepare the JUA application well in advance of the expiration of their present contracts.

Over the years, this agency has been a general agent of the Hartford Insurance group, and as a result, most of our volume of professional liability is in that company. We have been informed by them that effective June 1, 1977, they will no longer renew expiring policies. Policies in force will, of course, be allowed to run until expiration.

The St. Paul Insurance Company, one of the most experienced underwriters in this field, has entered into a contract with the Maine JUA to be the servicing carrier and administrator. All business will be transacted in the name of the JUA. The well equipped office in Boston that is presently handling the large

Massachusetts JUA for the past year, will be the Maine servicing office.

While the JUA may seem to be the answer to what has been a difficult situation during the past two years, there is one glaring and unfortunate feature, and that is the cost.

The present plan is to use the present rates which includes a higher factor for increased limits plus a 29% rate increase recently allowed the companies. On top of these increases will be the one-third of the premium surcharge mentioned earlier in this letter for the Stabilization Reserve Fund. Using limits of \$1,000,000/\$3,000,000, the yearly premium for a Class I doctor will be approximately \$2,100 and a Class VII doctor would be \$17,500.

I feel quite confident that all Maine agents handling this type of coverage will cooperate with the Maine Medical Association in making a smooth transition.

Your help in the past has been invaluable to this Agency. I hope we can justify your confidence in us, as the JUA plan goes into effect.

LAWRENCE DARR CHAPMAN  
Noyes & Chapman, Inc.  
One Canal Plaza  
Portland, Maine 04112

To the Editor:

The Pediatric Oncology Branch of the National Cancer Institute has a major interest in the study and treatment of rhabdomyosarcoma. Patients less than 25 years of age with all stages and histologic types of rhabdomyosarcoma or undifferentiated sarcoma are eligible, providing they have received no prior chemotherapy, radiotherapy or debulking surgery.

Although great strides have been made in the treatment of localized rhabdomyosarcoma, this progress has not been accomplished without significant morbidity. In this study, we will attempt to reduce surgically-related cosmetic and functional impairments in such patients by first shrinking the tumor mass with chemotherapy.

Unfortunately, patients with advanced or metastatic disease

remain especially difficult to treat and control. We plan to investigate the role of intensive escalating chemotherapy for such patients. This program will depend heavily on available supportive care facilities including laminar airflow rooms, hyperalimentation, transfusion support, and bone marrow rescue.

We request your cooperation in the referral of previously untreated patients with rhabdomyosarcoma and undifferentiated sarcoma to the Clinical Center, National Institutes of Health. Further information may be obtained from the Attending Physician, Pediatric Oncology Branch, National Cancer Institute, Building 10, Room 3B-12, Bethesda, Maryland 20014 or by telephone to (301) 496-4256. The Pediatric Oncology Branch also accepts patients with acute leukemia, non-Hodgkin's lymphoma, neuroblastoma, Ewing's sarcoma, and osteogenic sarcoma.

PHILIP A. PIZZO, M.D.  
WARREN E. ROSS, M.D.  
Pediatric Oncology Branch  
National Cancer Institute

To the Editor:

I am convinced that lives now needlessly lost to severe systemic reactions to insect sting could be saved by a greater awareness of both the possibilities of such fatal responses and of the existence of insect sting kits to be employed as emergency, first aid measures to stave off anaphylaxis. Because of this conviction, I am in the process of collecting and collating data on the incidence of such fatalities. I am especially interested in the time lapse between sting and death, although other information would also be greatly appreciated such as the following: time sequence of symptoms, previous reactions victim may have had to insect stings, whether and what medication the victim may have had on hand at the time of the incident, the type of insect if known, how many stings the victim may have suffered, and an estimation of whether or not a physician or hospital emergency room could have been reached in time to avoid a fatal outcome.

CLAUDE A. FRAZIER, M.D.  
4-C Doctors Park  
Ashville, N.C. 28801

## County Society Notes

### Cumberland

The Cumberland County Medical Society met on December 16, 1976 at the Red Coach Grill with 85 members present.

*Applications:* First Reading — Drs. Burton B. Knapp, Jr. and John H. Roediger. Transfer — Dr. Henry T. H. Grant. A reading was given for transfer of membership from the Hillsboro County Medical Society in New Hampshire for Dr. Henry T. H. Grant. It was voted to accept Dr. Grant in transfer.

#### *Correspondence:*

A letter from Dr. Brinton T. Darlington described a plan to develop a list of physicians who could be counted on to contact individual members of the legislature regarding bills in which the Medical Association is interested. Key bills will be related to malpractice and certificate of need. A list of legislators was circulated among the members present and fourteen of the forty names on the list were taken by members present at the meeting.

Letter from Pat Bergeron relative to nominations for special and standing committees of the Maine Medical Association — The various committees were mentioned by Dr. McAfee, and members were encouraged to let the secretary know of any interest in joining any of these standing or special committees.

#### *Old Business:*

Annual High School Scholarship Awards — A proposal to make an award of \$100.00 annually to a deserving senior student in every high school in Cumberland County received final discussion and was passed by a vote of the members present.

Physician's Directory — the members were reminded to complete their data sheets and return them to the Executive Office at

the Mercy Hospital.

Resolution on the death of Dr. Robert M. Morrison — the resolution, written by Dr. Donald J. McCrann, Jr. was read and accepted.

#### *Announcements:*

Announcements were made by Dr. Robert E. McAfee on the misuse of Tussionex,<sup>®</sup> the outcome of the recent meeting of the House of Delegates of the American Medical Association, and the fact that the withholding of medical records from other physicians until a patient's outstanding bill has been paid is unethical.

The meeting was adjourned at approximately 9:20 p.m.

The 409th meeting of the Cumberland County Medical Society was held at Union Mutual on January 20, 1977. It was the annual Member-Spouse Night and 232 members and spouses were present.

A cocktail hour was held, followed by a buffet meal after which a business meeting was not held. There was an announcement from Mrs. Eleanor Lovely about the book sale held annually by the Woman's Auxiliary. Following a few other introductory remarks and humorous comments by Dr. McAfee about the new Carter Administration, the speaker for the evening, Mr. Charles Dornan, was introduced and provided an evening of superb entertainment. After gaining participation from Drs. McCann, Hill, Branson, Klein and Contartese in this entertainment, the evening was brought to a conclusion on a pleasant note and all present considered the evening a great success.

WESLEY J. ENGLISH, M.D., *Secretary*

### Franklin

A meeting of the Franklin County Medical Society was held on February 7, 1977.

Report of French literature regarding diabetes availability from Dr. Melvin Bacon made.

Discussion MMA-MBA seminar invitation for March 17 at Augusta. Dr. David L. Phillips, our Executive Committee representative from Rumford, explained what it was; however, no members expressed an interest in participating. Dr. Phillips said similar disinterest has been noted amongst other County Societies. Letter to be written to Dr. O. Thomas Feagin thanking him for invitation.

Expense overrun on recent County Medical Society supper meeting discussed. Voted to reimburse the President, Dr. Paul A. Brinkman, for the cost overrun which he paid for out of his own pocket.

DANIEL K. ONION, M.D., *Secretary*

### Hancock

The Hancock County Medical Society held a meeting at the Tidewater Lodge in Trenton, Maine on February 23, 1977. Seventeen members were in attendance. Additional people in attendance included members of the Hancock County Dental Society, attorneys of Hancock County, and many wives. Total meeting attendance included 81 people. The guest speaker was Mr. Charles Cragin, III with other honored guests being Dr. and Mrs. Richard Leck.

After a convivial dinner, an excellent presentation of the malpractice situation in Maine was given in an address by Mr. Cragin. An excellent and informative question and answer period followed his address. As the hour was late at this time, a business meeting of the Society was postponed until another date.

WILLIAM C. BROMLEY, M.D., *Secretary*

### Kennebec

The January meeting of the Kennebec County Medical As-

sociation was held at the Holiday Inn in Augusta on January 20, 1977, with 44 members and one guest in attendance. The meeting was called to order by the President, Dr. James C. Hayes, and the minutes of the December meeting were read and accepted. The treasurer's report was read and accepted. The minutes of the Council Meeting of January 6th were read; no action was required upon them.

#### *Correspondence:*

A letter from Dr. Brinton T. Darlington, the Chairman of the Legislative Committee, was read reporting the designation of physicians who were familiar with the various State Legislators.

A letter from Dr. Richard C. Leck and Dr. Euclid M. Hanbury, Jr. was read concerning the joint Medical-Legal meeting in March.

#### *New Business:*

Applications from Drs. John Blasko and Marshall Chamberlin were read for the first time.

The report of the Nominating Committee was read and Dr. Richard E. Barron moved that the members of the Council be selected as delegates. Dr. Richard T. Chamberlin seconded the motion, and it passed. This required one additional delegate to be selected and Dr. Earle M. Davis was elected. The Nominating Committee was then charged with the responsibility for selecting a slate of alternate delegates.

The meeting was then turned over to Dr. Jose Castellanos who conducted a brief business meeting for the AMHI staff regarding some changes in their bylaws.

Dr. Hayes then introduced the speaker for the evening, Dr. Eugene Beaupre, the Maine Hospital Association representative on the Malpractice Commission. Dr. Beaupre presented the outline of the new Malpractice bill and urged the members of the Association to support it. There were several pertinent questions and the members were interested in the presentation.

The meeting adjourned at 9:30 p.m.

The Kennebec County Medical Association meeting was held on February 17, 1977 at the Silent Woman Restaurant in Water-

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ville. The meeting was called to order at 8:10 p.m. by the President, Dr. James C. Hayes. Previous minutes were read and approved.

Dr. Richard T. Chamberlin, our member of the Executive Committee, reported on the findings of the Medical Manpower Commission and introduced a resolution supporting a recommendation of the Governor and his Medical Care Development, Inc., assuming the leadership and coordination level for further development of manpower education programs in Maine. Considerable discussion ensued around this resolution. There seemed to be some question on the part of the members as to who were the controlling powers in the Medical Care Development, Inc., and just exactly what this resolution meant. The question was finally called and the resolution passed by a vote of 18 to 9.

Correspondence of the day included a letter from Dr. Hanley about the JUA. A letter from Paula Sawyer regarding the Bid Bug auction. Dr. Greene moved, and the members voted, to contribute two YMCA Health Club Memberships to the Bid Bug auction. Application of Dr. Bristol was read.

**Old Business:** A letter from Patti Bergeron was read indicating that we are eligible for 7 delegates. The Nominating Committee was informed of this and nominated Dr. Raymond E. Culver for the delegate. Alternate delegates who were nominated were: Drs. John H. Shaw, Martyn A. Vickers, Jr., George I. Gould, Peter J. Leadley, Joseph J. Hiebel, Howard H. Milliken and Meyer Emanuel. Final applications of Drs. Blasko and Chamberlin were read and accepted by the members.

Dr. O. Thomas Feagin introduced the speaker of the evening, Dr. Terrance McEnany, who presented a most informative and replete lecture on the subject of "Coronary Artery Surgery." Members responded with a great deal of interest and the meeting was finally adjourned at 10:00 p.m.

O. THOMAS FEAGIN, M.D., *Secretary*

### Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges Inn in Wiscasset, Maine on January 18, 1977.

There were twenty-two members and guests present.

The meeting was called to order by President Horstman at 8:25 p.m. The minutes of the December meeting were read by the secretary and accepted as read.

President Horstman announced the proposed format for meetings: Old Business, then a scientific speaker, then New Business. Several members debated the means of including all necessary and desirable business in the meetings of this Society. Dr. Richard C. Leck moved and Dr. Elihu York seconded the motion that this Society devote one meeting to Ladies Night, four meetings to socioeconomic issues, and four to scientific affairs. The motion was defeated. Dr. Dixon moved and many seconded the motion that dinner be served at seven o'clock instead of 7:30; the motion passed without opposition.

Dr. David W. Schall outlined the business discussed at the December meeting of the M.M.A. House of Delegates: Medicaid reimbursements to physicians were cut by an arbitrary ten percent; Blue Shield has reported its proposed improvements in contracts, with UCR programs and programs based on a fixed percentage of UCR as a ceiling, possible inclusion of some office laboratory fees, changes for medical emergency room visits, and office charges for plaster cast supplies; the Chief Medical Examiner outlines rules for certification of death; the M.M.A. was asked to intervene as *amicus curiae* in a suit against the State Dept. of Human Services revolving about dispute over necessity of Certificate of Need for a CAT scanner. Dr. Leck added that there is to be pressure Federally for extension of Certificate of Need to physicians' offices at the State level.

The secretary read a letter from the Kennebec County Medical

Association inviting this Society to attend a joint M.M.A.-Maine Bar Assn. meeting to be held in Augusta on March 17, 1977. Members were urged to attend and to notify the secretary at least a week before that of intention to attend.

Dr. William G. Wilkoff presented a CPC Pediatric slide show.

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held Tuesday evening, February 15, 1977, with twenty-nine members and guests present.

The meeting was called to order at 8:05 p.m. by the President, Dr. Anthony J. Horstman. The minutes of the January meeting were read by the secretary and accepted with one correction in a name.

Dr. Horstman read a letter from M.M.A. requesting the names of physicians unable to obtain professional liability insurance.

Dr. Bostwick mentioned two joint meetings of the M.M.A.-Maine Bar Association to be held in March: March 16th in Portland and March 17th in Augusta. Those planning to attend were asked to let the secretary know in good season.

Dr. Frank O. Avantaggio, Jr. introduced Dr. Robert Ritchie, of Portland, who spoke on Protein Chemistry and Plasma Analysis.

GEORGE W. BOSTWICK, M.D., *Secretary*

### Penobscot

The January meeting of the Penobscot County Medical Society was held on January 18, 1977 at the Mary Jane Restaurant in Bangor, Maine.

The meeting was opened by the President, Dr. John A. Woodcock, and the minutes of the previous meeting discussed and approved.

Under old business, members of the Society were solicited for assignment to individual State legislators as per Dr. Darlington's communication of last month. The list of assigned physicians and the legislators is being forwarded to Dr. Darlington.

The second Resolution for the House of Delegates meeting, that regarding perinatal facilities, was supported unanimously by the membership.

Under new business, the plans for a combined meeting with the Maine Bar Association in April for the Penobscot County group was noted and further information will be forthcoming. Dr. Woodcock will contact the other County Societies in this area.

A communication from the AMA regarding membership on councils was discussed. Anybody from the membership who is interested in filling vacancies on these councils is to notify the secretary.

A communication from Dr. Melvin Bacon regarding availability of diabetes information in French was noted.

The application for membership in the County Society for Dr. James F. Lawsing, III was unanimously approved.

Dr. Thornton W. Merriam, Jr. noted that the Executive Committee receives periodic reports of the activities of the Maine Legislature as they pertain to medicine. It was felt that this information should have greater distribution and it was moved that copies be sent from the central office of M.M.A. to the doctors' lounges in the various County hospitals, also to the various County physicians assigned to specific legislators (as per Dr. Darlington's communication).

It was also voted that the County Society make plans for reinstituting a newsletter.

Dr. H. Allan Hume, the Director of Emergency Medical Services for the State of Maine, then outlined his activities throughout the State, the funding of the various programs and the implementation of such. A lively question and answer period followed.

As there was no further business, the meeting adjourned at 9:30 p.m.

H. CLEMENT JURGELEIT, M.D., *Secretary*

### Piscataquis

The winter meeting of the Piscataquis County Medical Society was called to order by the President, Dr. Charles H. Stone, III, at 8:30 p.m., March 2nd at the Blethen House in Dover-Foxcroft, Maine.

Dr. Charles H. Lightbody discussed the activities of the last

meeting of the Maine Medical Association Executive Committee, including the proposed malpractice legislation and diagnosis of death. Dr. Linus J. Stitham brought up the topic of what to do about those County Medical Society members who chose not to pay dues to the State and therefore, according to the new regulations could no longer be members of the County Society. Various ways of including these physicians in activities of the County Medical Society were discussed but no conclusions were reached.

Following the brief business meeting, Dr. Hadley Parrot of the Tumor Clinic at E.M.M.C. led a discussion on the activities of the Tumor Clinic and on Advances in the Chemotherapy of Breast Cancer.

JAMES BERRY, M.D., *Secretary*

### York

The October meeting of the York County Medical Society was held on Wednesday, October 13, 1976 at the York Hospital, York, Maine. The program was as follows: Social Hour from 6:30 p.m. to 7:30 p.m. with the dinner, speaker and meeting following.

U.S. Representative David F. Emery, Rockland, Maine, Congressman 1st District, was the featured speaker of the evening giving an interesting talk on "Status of National Health Insurance." There was very active audience participation by the physicians present. It was replete with questions and answers. In closing, Congressman Emery stated he would welcome any suggestions, present or future, in which he could be of help to our Society. Dr. Richard C. Leck, President of the Maine Medical Association, who participated very actively added a quotation to this statement which was very apropos. Dr. Owen O. Dow then added his thanks and appreciation for Congressman Emery speaking to our group.

Our President, Dr. Lawrence Hazzard, then called the business meeting to order. In the interest of time, the minutes of the last meeting were dispensed with, as also were the minutes of the special meeting on Malpractice held at the Webber Hospital, Biddeford, Maine on Wednesday, September 15, 1976 with Dr. James Bonney of Portland, Maine who is both a physician and a lawyer as the featured speaker.

Under old business, Dr. Dow reappointed the same special committees to complete the year of 1976 as were selected for the fiscal year of 1975. The subject of Malpractice was again discussed.

The application of Dr. Patrick Crowley of Biddeford who is taking over for Dr. William O'Sullivan of Saco, was approved and he was accepted into membership.

It was announced that the Annual Diabetes Detection and Education Program would be conducted during the month of November. All hospitals in the county including the Goodall, Webber and York Hospitals would do urines free for glycosuria on anyone desiring it during this period. Mention was also made that these same hospitals would do blood sugars at a cost of \$2.00 on all patients referred by their family physicians from November 14th to the 20th. All county physicians would do urines free for glycosuria on anyone who requested this during this same period. These same institutions were also asked to do blood sugars on all their employees. All industries and nursing homes in the county will be contacted asking them if they desire to participate in this program by doing blood sugars on all their personnel. In instances where it is necessary, technicians from the Goodall Hospital Lab will be made available to collect the blood with sufficient material at a cost of \$2.00 each and the tests will be conducted at this hospital.

It was also announced that a precedent had been set at the Annual Meeting of the House of Delegates of the Maine Medical Association in June at the Treadway-Samoset at Rockport. For the first time in the history of the York County Medical Society, the newly elected president and the past president attended. In addition, the newly appointed member and the outgoing member of the Executive Committee were also present. I am also happy to say that all three delegates and your secretary were there.

The following announcements were made. First, the Annual Meeting of the York County Medical Society will be held on Wednesday, January 12, 1977 with the place and time to be

announced at a later date. Secondly, the fall meeting of the House of Delegates of the Maine Medical Association will be held at the Mid-Maine Medical Center (Thayer Unit), North Street, Waterville, Maine on Sunday, December 12, 1976, with registration at 12:30 p.m.; Dinner at 1:00 p.m., and Business Meeting at 2:00 p.m. The third announcement was a Workshop on Neurology for nurses will be held at the Hilltop House, Nasson College, Springvale, Maine on Monday, October 18, 1976.

A report of the House of Delegates Meeting held at the Treadway-Samoset Resort in Rockland in June was given by Dr. Carl Richards. He reported that Dr. Donald Anderson of Lewiston was voted President-elect of the Maine Medical Association and that Dr. Maurice Ross of Saco was elected to the Executive Committee for the 1st District. He also discussed the resolutions which were acted upon. These included membership in the

county society, one by the ENT group, the selection of an Assistant Executive Director of the Maine Medical Association, a rather extensive 14 point item brought up by Dr. Shields and another on continuing education. He also mentioned that the movement for a medical school in Maine is not dead.

There was no correspondence of any significance. There were 25 physicians and 3 guests present. May I state it was a distinct privilege and pleasure to have Dr. Richard Leck, President of the Maine Medical Association and Mrs. Leck as our guests. We all welcomed the active participation of Dr. Leck in so many phases of this meeting.

Jim McMahon of Congressman David Emery's office also attended this meeting.

The meeting was then adjourned at 9:45 p.m.

MELVIN BACON, M.D., *Secretary*

#### THE PREOPERATIVE REVIEW — Continued from Page 193

be started if any untoward events delay his return to oral feeding.

*Problem #6*, Prednisone therapy.

*Subjective*: Zero.

*Objective*: No signs of Cushingoid syndrome. He has been on 8 mg. of Prednisone per day for several years.

*Assessment*: I expect his adrenals to be unresponsive to stress.

*Plan*: IV Medrol® to be started in first infusion preoperatively.

"Other problems are inactive or do not bear upon this procedure."

The preoperative note need not be written when the patients are admitted for elective surgery, as the

admitting history and physical would accomplish this. It is most applicable to patients who are hospitalized for some time for diagnostic studies, and then undergo surgery. If the diagnosis turns out to be wrong, the poor thinking in reaching it is obvious to all. This can be a humiliating experience.

I would urge all surgeons to undertake themselves or to assign to a high ranking surgical resident the writing of such a note 24 hours prior to surgery.

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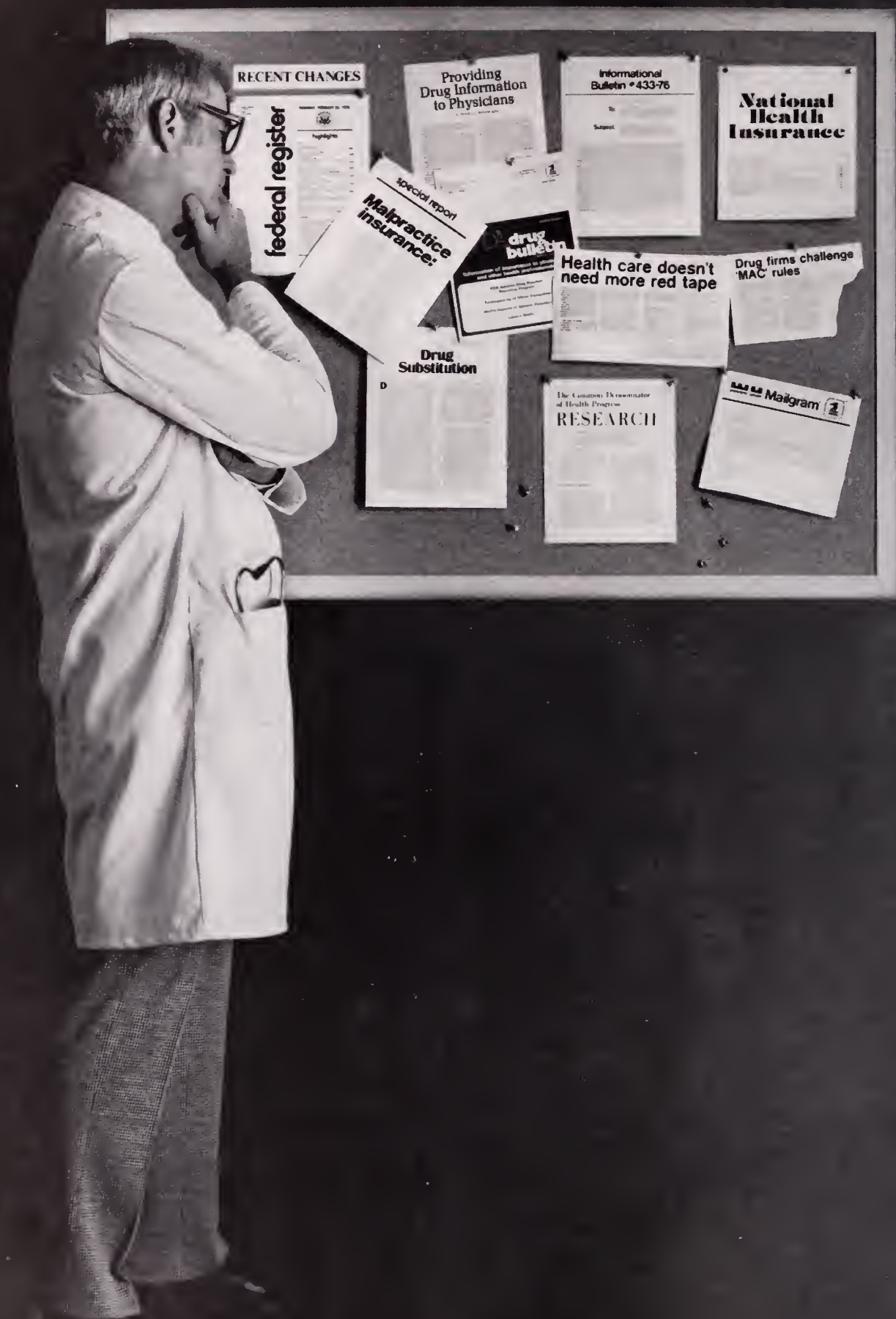
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# The Journal of the Maine Medical Association

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## Sudden Coronary Death

JACOB B. DANA, M.D.\*

There is on occasion, on the part of some physicians, a nihilistic attitude about preventing or delaying sudden death which is death occurring within 24 hours of the onset of symptoms in someone previously active in the community.

The question is, of course, when is sudden death premature? Dr. Howard Burchell defines "premature" as ten years older than he is. A nihilistic attitude about prevention does not help at any stage of medical undertakings. The nihilistic argument is surely not a valid one for progress in cardiology.

What is the burden of sudden death to the community? We do and will have a tremendous burden as illustrated by 165,000 sudden deaths in people under age 65 in 1973.

To what extent metabolic and/or functional mechanisms underlie the pathophysiology of sudden cardiac death is yet to be determined. The possibility that fine ultra-structural changes at the membrane and subcellular levels may be implicated has to be rigorously examined.

Because of the social and economic implications of sudden cardiac death and the need to embark upon both primary and secondary prevention programs, pathophysiologic bases of this complex problem need critical reappraisal.

The studies of Kuller, Cooper and Perper on the extent of coronary pathology and sudden atherosclerotic heart disease deaths has depressing therapeutic implications. Coronary atherosclerosis in the majority of these cases is a diffuse, severe, multi-vascular process frequently associated with chronic myocardial damage. Single artery disease is a relatively infrequent finding. No significant intramyocardial blood vessel disease could be demonstrated in their studies of sudden coronary death. The extent of disease of the coronary vessels and

associated myocardial pathology suggests that only therapeutic modalities that will prevent the development of coronary stenosis or decrease the extent of existing coronary artery disease by medical or surgical techniques have the potential for long-term benefit to the patient.

In another study of the myocardium and the conduction system in sudden coronary death, the prevalence of cardiomegaly and significant coronary atherosclerosis and the relative infrequency of acute coronary thrombosis in pre-hospital sudden coronary death was reaffirmed. Sixty-two to 74 percent of the cases had either acute or old myocardial infarctions. Evidence of acute myocardial ischemia, as determined by histologic criteria of myofibrillar degeneration and other features, was present in 52 to 81 percent of the cases. Some of the demonstrated myocardial infarctions were as old as 4 weeks and others less than 24 hours. The high incidence of myocardial ischemia is compatible with the proposed mechanism of sudden coronary death, namely, ventricular fibrillation or asystole, and underscores the importance of presymptomatic diagnosis. No specific or acute anatomic lesions in the conduction system have been demonstrated. However, this does not preclude the possibility of a bradyarrhythmia occurring shortly before death.

### PROFILE OF HIGH RISK IN PATIENTS KNOWN TO HAVE CORONARY DISEASE

One study found that 95 percent of patients with sudden cardiac death occurring within 5 years after myocardial infarction could be correctly identified on the basis of four variables: 1) Cardiomegaly; 2) Diastolic hypertension; 3) Congestive heart failure; 4) Cigarette smoking.

One prospective study was carried out in which 100 patients were followed based on the presence or absence of premature ventricular contractions on a predischarge 6-hour electrocardiographic tape.

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In those without significant ventricular premature beats, 91 percent of both the survivors and the non-survivors were correctly identified by the combination of bigeminy, VPB prematurity, VPB frequency, and finally the age of the patient. In the group in which VPBs were present, 75 percent of the survivors and 100 percent of the non-survivors were properly classified.

The prognostic importance of in-hospital VPBs and in their identification of patients who are apt to suffer an increased mortality during the subsequent post-hospital period is stressed. Patients with no VPBs or less than 20 per hour but without multiform or bigeminal beats had a combined cardiac death and reinfarction rate of 8 percent within 4 months of discharge. Those with more than 20 VPBs per hour, or with multiform or bigeminal beats had a complication rate of 31 percent in the 4-month period. This was 4 times greater than the low risk group.

In patients with neither prior myocardial infarction nor advanced New York Heart Association functional state before the index event, the presence of two or more clinical factors (1. history of increased blood pressure, 2. cardiomegaly, 3. digitalis treatment at discharge) identified a subgroup with 26 percent complication rate in a 4-month period of follow-up.

If there was prior myocardial infarction or advanced New York Association classification, two or more factors (1. cigarette smoking, 2. hypotension in the Coronary Care Unit, 3. predischARGE high risk VPBs identified patients with a 41 percent incidence of post-hospital complications in the succeeding four-month period.

In the coronary drug project, a combination of 5 coded ECG items — 1) presence of an infarct Q-wave, 2) resting ST segment depression, 3) ventricular conduction defects, 4) atrial fibrillation, 5) ventricular premature beats — was used to classify patients who showed a seven-fold range of increased mortality risk.

#### PRODROMES OF SUDDEN DEATH

In this area, one has to rely on second-hand evidence. On the basis of such evidence, it would appear that many of these patients in whom some data is obtainable had few complaints of chest pain but more complaints of fatigue and dyspnea. It is obvious that a prospective type of study is needed.

Data from 981 evaluations for ischemic heart disease with angiography were reviewed in an effort to identify variables that might be predictive of sudden death and the duration from onset of symptoms to the fatal episode. One hundred and thirteen patients died during the follow-up period. Ninety-nine of these deaths were classified as cardiovascular. Forty percent were dead within 1 hour of the development of signs or symptoms, an additional 34 percent were dead within 24 hours, and an additional 25 percent were dead in more than 24 hours. The best 5 variable model which might predict sud-

den death in these patients included the following variables: 1) number of vessels with greater than 70 percent obstruction; 2) the therapeutic requirement of inotropic and diuretic drugs; 3) premature beats; 4) ventricular conduction defects.

Thus, we do have some possibility of identifying patients prone to sudden death.

#### PROFILE OF RISK OF SUDDEN DEATH IN APPARENTLY HEALTHY PEOPLE

There is general agreement that sudden death in the United States is almost invariably due to coronary disease. If one extends the time interval from onset of the symptoms or signs up to 24 hours, 14 percent of the sudden deaths are related to alcoholic liver disease on the basis of Kuller's study. The frequency of acute myocardial infarction is variable, and the heart weight of people who die suddenly and unexpectedly is often increased.

In retrospective studies of sudden death, about one-half of the victims have had known heart disease, usually ischemic; they are mostly male. The risk appears to increase with age; the presence of hypertension and diabetes mellitus is frequent, and heavy cigarette smoking is common.

In most, there is no precipitating lethal event, though a significant number of patients or victims had, shortly before, engaged in moderate or strenuous exercise.

Without supporting evidence, the disclosure of premonitory symptoms has been assumed to invoke the possibility of life-saving intervention. In Kuller's study, 38 percent of the patients, and in another study from Edinburgh 40 percent, had sought medical attention in the 2- to 4-week period prior to death. The symptoms of which these people complained included fatigue, breathlessness, chest pain and cough. In many instances, the symptoms were vague, and it would be hard to infer from them, the presence of coronary disease.

In the first 14 years of the Framingham Heart Study, two-thirds of those dying within one hour of onset of symptoms died outside the hospital. Nearly one-half of these people had no prior clinically apparent heart disease. Meticulous inquiry failed to yield evidence that these individuals had reported to anyone prodromes that could have been construed as symptoms of coronary heart disease. However, the risk profile was identical with peer groups deemed to be at increased risk of coronary disease or who had survived a myocardial infarction. Hypertension, an electrocardiographic pattern of left ventricular enlargement, gross obesity, and heavy cigarette smoking were all strongly correlated with an increased risk of sudden and unexpected death.

It may be concluded that the risk of sudden death is synonymous with those factors associated with an increased risk of atherosclerosis. The therapeutic and prophylactic implications are the same.

Sudden death is thought to be due almost invari-

ably to ventricular fibrillation. Death rate is highest early in the course.

There has been much discussion over the implications of premature ventricular beats, but they probably do not have adverse prognostic significance in the absence of other manifestations of cardiovascular disease.

Hinkle made a study of continuous tape recordings of the electrocardiogram during standard work and activity patterns. This study included 301 middle-aged males. Ninety-three percent showed asymptomatic periods of dysrhythmia or defective AV or IV conduction. Ventricular premature contractions and complex ventricular dysrhythmias occurred in 62 percent, and transient or fixed abnormalities of conduction in 7 percent, most often in men with established coronary artery disease or those exhibiting one or more coronary risk factors, and these were associated with an increased risk of sudden death. With the passage of time, this group exhibited so-called sustained relative bradycardia.

The presently available treatment of the metabolic and electrophysiologic precursors of atherosclerosis, myocardial infarction, and sudden death are to some extent of unproved effectiveness. The primary prevention of atherosclerosis is inevitably the most rational approach to the prevention of sudden unexpected and premature death. Sudden death, the most dramatic expression of end-stage disease, should not divert us from our highest priority, which is to invest most of our finite resources in attempts to learn how to suppress, to delay, or to minimize atheropoiesis. However, it is a mistake to regard secondary prevention as contradicting the need for primary prevention or the converse. The clinician must orient not only to the necessary but also to the possible. It is now becoming possible to prevent sudden death.

#### **PRIMARY PREVENTION OF SUDDEN CORONARY DEATH**

The contemporary epidemic of premature sudden death, along with its underlying pathologic basis, severe atherosclerosis, is due fundamentally to the evolution of the 20th century life style. Socio-economic development has led to the replacement of tuberculosis by coronary disease as the big mass disease of the adult population. The coronary epidemic, like the tuberculosis epidemic, is essentially societal in origin.

It is due particularly to the evolution of nutritional habits and smoking habits, aided and abetted, in all probability, by the concomitant emergence of sedentary living habits and possibly by personality and behavioral patterns that are common in modern industrial society.

If this view is correct, then prevention of sudden death and especially primary prevention must be viewed as a societal task related first and foremost to improving life style. An inevitable corollary is that pharmacologic approaches must be seen as second-

ary and adjuvant, no matter how good the benefit to risk ratio.

In a prospective study of 1600 employees of the Peoples Gas Co. of Chicago, the participants were divided into three groups: 1) those free of coronary heart disease; 2) those suspected of having coronary heart disease; 3) those with definite coronary heart disease. During the first 10 years of follow-up, mortality rate from sudden death was 19 per thousand in those free of coronary heart disease, 29 per thousand in those suspected of coronary heart disease and 126 per thousand in those with definite coronary heart disease. Sudden deaths represented one-half of all coronary deaths. In those with definite coronary heart disease, sudden death made up 40 percent of all deaths that occurred. Obviously, and this has been mentioned before, the risk of sudden death, sizeable as it is for middle-aged men free of coronary heart disease, is far greater for those with clear-cut evidence of coronary heart disease.

With these facts in mind, it is appropriate to define primary prevention of sudden death as the prevention of the event for the great majority of the young adult and middle-aged population which is free of evidence of coronary heart disease and generally well clinically.

In the Peoples Gas Co. Study, 903 participants had no evidence of any disease. Electrocardiograms (done without exercise) were normal. The group was compared with 557 with organ system disease on the basis of three major risk factors: 1) hypercholesterolemia, with a cholesterol of greater than 250 mgs.%; 2) hypertension with a diastolic blood pressure greater than 90mm./mercury; 3) cigarette smoking of greater than 10 per day.

There were 30 sudden deaths among the 903 participants apparently free of disease over a 15-year period. This calculates out to 33.8 deaths per thousand. There were 42 sudden deaths among the 557 participants with organ system disease, and this calculates out to 62.8 deaths per thousand. The 557 with organ system disease accounted for 58.3 percent of sudden deaths, though making up only 38 percent of the overall group.

For the 903 originally free of any evidence of organ system disease, the risk of sudden death was strongly related to the three major risk factors. Those free of these risk factors had no sudden deaths in the first 10 years of follow-up and only 3 over the next 5 years, giving an age-adjusted rate from sudden death of 13 per thousand. If any one risk factor was present, or any two, or all three risk factors were present, the 15-year mortality rate from sudden death was 3 times greater. Corresponding conspicuous differences were recorded for mortality from all coronary heart disease, all cardiovascular disease, and from all causes, with the group having two or three risk factors present exhibiting the highest death rate at 5, 10 and 15 years.

Other studies confirm these findings and show that each of these factors make an independent contribution to risk. With modern methods of statistical analysis one could classify even more precisely those at the greatest risk of sudden death.

The next conclusion and inference follows logically. It is likely that the rate of development of the underlying disease, severe atherosclerosis, can be influenced by influencing these three major risk factors with the consequent achievement of primary prevention of sudden death. This idea is all the more attractive since the key approaches to prevention involve safe, nutritional and hygienic changes. These include improvement in life style, such as cessation of cigarette smoking, better eating habits aimed at lowering serum cholesterol and decreasing blood pressure, with modern tested drug treatment of hypertension an additional aspect of the preventive approach when such an approach is specifically indicated. The logic of such a position is unassailable but may not be true to life, and this has to be proved. Hopefully, things like the multiple risk factor intervention trial and hypertension detection and follow-up program will yield significant information. In the meantime, the best judgment indicates the wisdom of proceeding with preventive efforts, especially for high risk people.

A further question arises concerning the implications of the foregoing data. What about the impact of major risk factors for those who already have organ system disease? Do the available data suggest that they are still reasonable candidates for this kind of nutritional and hygienic approach to prevention, or is it too late? At any point in life, the more of these risk factors that are present, the more likely a person is to show cardiovascular organ system disease or to subsequently develop signs of pathology.

Moreover, when organ system disease is already present, the risk factors continue to relate to risk of sudden death as well as death from all cardiovascular disease and all other causes. Death rates are lower if there are no risk factors present despite the presence of organ system disease.

The implications are obvious. There is a potential for prevention for such persons, even though organ system disease is already manifest including signs of atherosclerosis. Therefore, while emphasizing primary prevention and its strategic importance in terms of the effort to bring the epidemic of premature sudden death in coronary heart disease under control, one must add that the available evidence leads to the encouraging conclusion that it doesn't serve much purpose to make a sharp distinction between prevention for those with and those without manifest organ system disease as long as one doesn't lose sight of the importance of going beyond those already ill to the population at large and especially to the high risk people.

This conclusion concerning the possibility of preventing sudden death and prolonging life, even for those already stigmatized by frank clinical coronary

disease, through intervention against the major risk factors (increased cholesterol, gross obesity, cigarette smoking) especially in those amenable to safe, nutritional, hygienic measures, is supported by the findings in a group treated with placebos in the coronary drug project. Therefore, even for persons with definite myocardial infarction, at least middle-aged men in functional group I and II, there is a potential as a logical inference through risk factor intervention to change the course of the disease and prevent sudden death and prolong life.

How early in life is it possible to identify high risk people? On the basis of the University of Pennsylvania and Harvard student studies on students who are studied at entrance into college, in those who smoked more than 10 cigarettes per day or had a systolic blood pressure greater than 130, mortality rate was 1.6 for the smokers and those with increased systolic blood pressure and 2.1 for those with both risk factors on follow-up at 20, 30, and 40 years. Thus, the ability to detect high risk persons early, at least by the second decade, is substantial and since there is a tendency for these traits to show familial aggregation identification of an index case gives a lead to others.

Again, the logical inference follows that institution of early preventive improvement in life style clearly has the best chance of success.

What actual evidence is there, as distinct from logical inference, that such preventive approaches will work?

There are a variety of studies which provide such evidence. There is the V. A. Hypertensive Study which demonstrated a decreased incidence of strokes when treatment for hypertension was instituted, and there is much data on the effect of change in eating habits on coronary atherosclerosis. This effect has been demonstrated mainly in studies which show a reversal of previously produced atherosclerotic lesions in the monkey.

So far as diet in humans is concerned, one valuable set of data comes from a carefully designed trial done at a V. A. domiciliary installation in California. One group of patients in this study had the usual American diet and one group a fat-modified diet, with a reduction in saturated fat and cholesterol and an increase in poly-unsaturated fat. In 422 control patients and 424 patients on fat-modified diets, the number of sudden deaths over more than 8 years of follow-up were 27 in the controlled group and 18 in the low-fat diet group, a 33 percent lower rate in the fat-modified diet group. The median age of these men was 65.5 years. When they were stratified by baseline age and serum cholesterol levels and cumulative incidence curves for a set of hard end points were evaluated, evidence emerged for efficacy of the fat-modified diet, particularly for younger men with increased levels of cholesterol.

As to cigarette smoking, it is relevant to look at some autopsy material. It is evident that cigarette smoking significantly influences the development of

severe atherosclerosis, the pathologic process underlying the majority of instances of sudden death. Its effect is not primarily an acute one precipitating sudden death; it is a long-term effect related to the basic disease process. There is some confusion about this in the literature.

What are the effects of cessation of smoking? No data is as yet available from a randomized control trial but there is evidence from population studies dealing with people who have changed their smoking habits compared with continued users and this evidence demonstrates a lower rate of coronary heart disease, sudden death, and death from all causes.

Again, the studies of Dorn comparing the mortality experience of non-smokers, those who continued to smoke at the beginning of the study in 1954 and those who had quit smoking is of interest. Again, there is impressive evidence indicating that it does pay to stop smoking, as indicated by the mortality statistics.

This now is the situation. We have a large amount of consistent data on the powerful impact of the major risk factors, data from multiple studies on man backed by confirmatory animal experimental evidence. There is also extensive evidence that the major risk factors can be influenced by safe, nutritional, hygienic means supplemented, when necessary, by drugs for the treatment of hypertension.

We have suggestive data that intervention of this kind, effectively sustained for years will reduce the rate of development of clinical atherosclerotic disease, including sudden death.

Meanwhile, medical and public health practice must proceed to cope with an epidemic problem, using its best judgment based on the available evidence. Every responsible group that has examined this problem over the last decade — American Heart Association, Council on Foods and Nutrition of the American Medical Association, the Inter-Society Commission for Heart Disease Resources and many others — have all urged that as a nation we cease to temporize and begin to act to control the epidemic.

Where do we stand in regard to acting on these recommendations and changing the situation? This brings us face to face with the social problems and responsibilities of the investigative community and the heart community to address the social problems

more vigorously, particularly the problem of cigarette smoking.

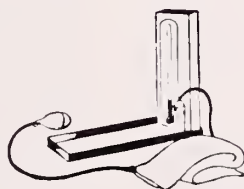
Finally, the emphasis on nutritional, hygienic approaches for both those with and without evidence of organ system disease does not preclude adjuvant use of pharmacologic approaches with known and proved favorable benefit to risk ratio.

Two complementary approaches to the prevention of sudden death should not be pitted one against the other.

Clauswitz, as quoted by Stamler, taught many years ago that in fighting a war the first prerequisite is a sound strategy. Viewed overall, the effort to control the coronary epidemic requires a sound strategic approach by our society as a whole. Our knowledge about this disease compels the conclusion that the main strategic thrust must be improvement of life style on a broad societal basis and as early as possible.

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# The Effect of Intra-Peritoneal L-Methionine on the Development of Steroid Ulceration in the Rat

FENNELL P. TURNER, M.D.\* and VICTOR C. BRUM, Ph.D.†

## INTRODUCTION

Acute gastric erosions were demonstrated in the adrenalectomized animal by Cioffi in 1905.<sup>1</sup> Similar observations were made later by others and in 1934 Selye<sup>2</sup> stated that acute gastric ulcerations were characteristic of the alarm reaction. In 1951, Turner<sup>3,4</sup> suggested that the adrenal gland may play two somewhat opposing roles in the pathogenesis of stress ulceration: First, an important role in the regulation of cellular and capillary permeability. Therefore an adequate supply of adrenocorticoids might be necessary to protect the gastroduodenal mucosa against the development of the acute gastric erosions and tiny ulcerations sometimes seen immediately after injury. Second, it was surmised that high adrenal activity may alter the synthesis or availability of sulfated mucosubstances thereby impairing wound healing. We proposed at this time that the development of peptic ulcer in all of its many clinical variations (acute, chronic, gastric, pyloric and duodenal) might in some way be related to sulfur-containing nutrients.

Pappenheimer and Larimore in 1924<sup>5</sup> first called attention to the occurrence of ulcers in the fore-stomachs of rats maintained on deficient diets. In more recent years, observers have described the presence of ulcerations in the glandular stomach following the administration of adrenal steroids. Such ulcers were reported by Ingle in 1945<sup>6</sup> and subsequent observations were made in 1951<sup>7</sup> which were confirmed by other laboratories.<sup>8,9,10,11</sup>

It was at this time that we initiated our first clinical study<sup>12</sup> on the treatment of peptic ulcer with DL-methionine. The results of this study suggested strongly that supplemental methionine was beneficial in the treatment of peptic ulcer. It was apparent also from these clinical studies that an animal model for gastric ulceration might prove useful in elucidating basic cellular mechanisms of steroid ulceration which in turn might offer some correlation with human peptic ulceration and the role of sulfur donating substances. Our observations upon the role by sulfur donors on induced gastric ulcerations in the rat are presented.

## METHODS AND MATERIALS

Young male Sprague-Dawley rats (6-8 weeks old) were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Mass. The animals were caged individually upon receipt and observed until mature weights (300-400 grams) were reached, unless otherwise noted in the text. In the pre-fasting period all animals were maintained on Purina<sup>®</sup> laboratory chow containing 0.43% methionine w/w for 4-5 days. During this period, the average consumption of food and water per animal was 20-25 grams and 5-10 ml respectively.

During the period of experimentation, animals were placed on either (1) normal laboratory diet (Purina Laboratory Chow); (2) Sidransky diet for sulfur depletion;<sup>13</sup> (3) fasting with water ad libitum; (4) fasting with salt, sugar and vitamin supplementation. The composition of this latter supplementation was as follows: 5% Dextrose in normal saline with 4 drops of vitamins (Zymadrops,<sup>®</sup> Upjohn) added to 250 ml of above solution.

Solutions of L-methionine, and L-threonine were prepared in physiological saline (w/v) and stored at 4°C. These were given intraperitoneally (2 ml daily for seven consecutive days) in the concentration noted in the text. In one series for a total period of five days, a 1% aqueous solution of DL-methionine was provided as drinking water. The average amount consumed daily was from 50 to 100 mg. Corticosteroids were administered either as cortisone acetate (Merck, 10 mg; subcutaneously daily per animal or as methyl prednisolone acetate Upjohn, 6 mg; intramuscularly daily per animal). All injections were made daily during the experimental phase of the investigation. All ulcerations were evaluated by their gross pathological appearance, enumerated, and the results expressed as percent of animals with ulcers.

## RESULTS

Our initial studies confirmed the findings of others that fasting induced ulceration in the rumen of the rat. When cortisone acetate was administered to the fasting animal ulcerations were now primarily confined to the glandular stomach (Table 1). A 5-day fasting period with cortisone acetate was found to be more effective in producing gastric ulceration than was a period of four days. This data also suggest that small rats are more prone to gastric ulceration than larger rats and that any diet, or supplementation

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TABLE 1

THE EFFECT OF SIZE AND EVENTUAL WEIGHT LOSS ON THE DEVELOPMENT OF GLANDULAR ULCERATION									
Program	No. of Days	No. of Animals	Initial Wt. Average	in Gms. Range	Wt. Loss Average	in Gms. Range	Percent Wt. Loss	No. with Ulcers	Percent
Fasting and Cortisone Acetate	4	10	156±4.0	150-162	52	44-63	33.0±13.9	0	0
Fasting and Cortisone Acetate	5	10	108±9.4*	92-121	46	40-53	42.4±2.2	10	100
Fasting and Cortisone Acetate	5	19	145±19.5	123-200	58.5	46-76	39.4±2.2	7	36.8

\*Mean values ± standard deviation

TABLE 2

THE EFFECT OF SULFUR DEPLETION DIET ON THE DEVELOPMENT OF ULCERS IN GLANDULAR STOMACH									
Program	No. of Days	No. of Animals	Initial Wt. Average	in Gms. Range	Wt. Loss Average	in Gms. Range	Average % Wt. Loss	No. with Ulcers	Percent
Sidransky Diet (Cortisone acetate subcutaneously on 7 of last 9 days)*	25	10	172±38.5 +	(116-226)	74	(56.0-104)	46.2±3.4	1	5.0
Sidransky Diet Fasting (Cortisone acetate subcutaneously daily for 4 days)	14								
	4	14	153±17.0	(125-182)	66	(51.5-83)	43.1±3.1	13	98.8

\*These animals were not fasted.

+Mean values ± standard deviation.

TABLE 3

THE EFFECT OF GLUCOSE, VITAMINS AND METHIONINE SUPPLEMENTATION ON THE DEVELOPMENT OF GLANDULAR ULCERATION									
	No. of Days	No. of Animals	Initial Wt. Average	in Gms. Range	Wt. Loss Average	in Gms. Range	Average % Wt. Loss	No. with Ulcers	Percent
Fasting and Cortisone Acetate	5	10	108±9.4**	92-121	46	40-53	42.4±2.2	10	100
Fasting, Cortisone Acetate and 1% DL Methionine P.O.*	5	9	106±24.3	65-126	43	30-54	41.0±3.0	9	100
Fasting, Cortisone Acetate, salt, sugar and vitamins	5	9	107±35.0	61-161	31	22-48	28.0±2.4	5	55.5
Fasting, Cortisone Acetate, salt, sugar, vitamins and 1% DL Methionine P.O.*	5	9	104±35.0	61-156	27	19-47	26.0±3.2	4	44.4

\*500-100 mg. DL Methionine per day added to drinking water.

\*\*Mean values ± standard deviation.

(glucose and vitamins) to fasting conditions offers protection against the development of steroid ulceration (Tables 2 and 3). There also appears to be a correlation between weight loss and ulcerations since nearly 100% of the animals with a weight loss of 40% or more developed ulcerations (Table 1, 2, 3). Animals in groups with average weight losses of less than 40% showed fewer ulcerations. Sulfur depletion effected with a Sidransky diet<sup>13</sup> followed by 4 days of fasting and steroid administration further increased the incidence of gastric ulceration to 98.8% (Table 2). It should be pointed out that only one of ten animals that were depleted with Sid-

ransky diet but never fasted developed glandular ulceration.

The administration of 1% DL-methionine to the water of fasting animals had no significant influence upon the incidence of ulceration.

Subsequent studies administering L-methionine intraperitoneally to fasting animals that received methyl prednisolone intramuscularly proved more rewarding. Forty animals were studied. These animals were divided into four groups of ten each. Here it was found that the ten animals that had received 4% methionine had the fewest number of glandular ulcerations (Table 4). It was observed, also, that the

ulcers on the average were slightly smaller and the total calculated area of gastric ulceration was less in those animals treated with methionine than in the

control animals (Tables 5 and 6). Finally, weight loss (Table 7) differences in the 4 treatment groups were not found to be significant.

TABLE 4

STERIOD* ULCERATION IN THE FASTING WHITE RAT				
Intraperitoneal Treatment Program	A N-saline	B 2% Meth.	C 4% Meth.	D 2% Threo.
No. of Animals in Group	10	10	10	10
Animals with 9 Ulcers or Fewer	6	6	9	4
Animals with 10 Ulcers or More	4	4	1	6
Total Ulcers in all 10 Animals of each Group	71	77	54	102

\*Methyl Prednisolone 6 mg. IM daily, each animal.

TABLE 5

DISTRIBUTION OF ANIMALS ACCORDING TO SIZE OF LARGEST GLANDULAR ULCER IN EACH ANIMAL				
Group	A N-saline	B 2% Meth.	C 4% Meth.	D 2% Threo.
No. of Animals	10	10	10	10
0 ulcer	0	0	1	0
Size of largest ulcer (in mm.) in each animal				
1 to 3 mm.	4	7	6	4
4 to 6 mm.	4	2	2	4
7 to 9 mm.	1	0	0	1
10+ mm.	1	1	1	1

TABLE 6

EXTENT OF MUCOSAL ULCERATION IN MM <sup>2</sup> ACCUMULATED TOTAL IN EACH GROUP OF 10 ANIMALS				
	A N-saline	B 2% Meth.	C 4% Meth.	D 2% Threo.
No. of Animals	10	10	10	10
Minimum estimate of involvement*	250	205	196	278
Maximum estimate of involvement+	1658	1240	1084	2198
Total ulcers in 10 animals in each group	71	77	54	102

\*MM<sup>2</sup> of ulcerated surface of largest ulcer added to 1 MM<sup>2</sup> (arbitrarily chosen as smallest visible ulcer) multiplied by number of total number of ulcers found.

+MM<sup>2</sup> of ulcerated surface of largest ulcer multiplied by total number of ulcers in each animal.

## DISCUSSION

These experiments whereas not statistically significant, suggest that intraperitoneally administered L-methionine will counteract partially the deleterious effects of adrenal steroids in the fasting rat. It is hypothesized that supplemental methionine in the steroid treated fasting animal may have this beneficial effect, either because of its contribution to the metabolism of gastric epithelium or by assisting in the eventual sulfation of the acid mucopolysaccharide fraction of gastric mucin. Histochemical studies of gastric mucosa and of the various enzyme systems present in the rat stomach, as well as radioisotopic labeling studies of their products, may help to further elucidate the mechanism responsible for our observations.

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TABLE 7

WEIGHT LOSS ASSOCIATED WITH ADMINISTRATION OF ADRENAL STEROIDS* IN THE FASTING WHITE RAT				
Group	A N-saline	B 2% Meth.	C 4% Meth.	D 2% Threo.
No. of Animals	10	10	10	10
Initial wt. in gms.	3-11	315.0±14.0**	315.0±14.0	304.0±19.2
	3-16	343.0±15.0	343.0±18.0	339.0±24.9
Av. wt. loss (gms.)	3-16 to 3-23	146.0±7.0	142.4±10.5	148.0±18.1
Av. wt. loss (%)	3-16 to 3-23	42.5±1.8	41.6±2.1	43.5±11.4

\*Methyl Prednisolone

\*\*Mean values ± standard deviation

# Incorporation of $^{35}\text{S}$ L-Methionine by the Rat With Steroid Ulceration

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## INTRODUCTION

Acute gastric erosions in the glandular stomach of the rat were first described following administration of adrenal steroids in 1945.<sup>1</sup> The first clinical report of gastric ulceration in a patient receiving ACTH was made in 1950.<sup>2</sup> Many observations and experiments have been made in the succeeding years and steroid ulceration has remained a controversial subject.<sup>3</sup> Recently, we reported observations suggesting that the intraperitoneal administration of 4% L-methionine in small daily doses will reduce the number and severity of acute steroid ulcerations in the white rat.<sup>4</sup> The purpose of this paper is to report our observation on changes in the incorporation of  $^{35}\text{S}$  methionine in the animal with steroid ulceration under different experimental conditions.

## MATERIALS AND METHODS

Nineteen young male Sprague-Dawley rats (6-8 weeks old), weighing between 125-135 gms., were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. L-methionine was obtained from the Nutritional Biochemical Corporation of Cleveland, Ohio. Radiolabeled  $^{35}\text{S}$  methionine, specific activity 227.3 Ci/mmol (1.0 mCi in 0.2 ml aqueous solution) was obtained from New England Nuclear, of Boston, Massachusetts.  $\beta$ -glucuronidase ( $\beta$ -D-Glucuronidase glucuronohydrolase E. C. no. 3.2.1.31) 0.625 gms  $\approx$  800,000 Fishman Units  $\pm$  1 gm) was obtained from Sigma Chemical Company. Phenolphthalein glucuronic acid (PGA), 100 mg, was used as the enzyme substrate in the  $\beta$ -glucuronidase assay method, and was also obtained from the Sigma Chemical Company. Depo-Medrol methylprednisolone acetate (6 $\alpha$  methylprednisolone 21-sodium acetate: 11 $\beta$ , 17 $\alpha$  21 trihydroxy-6 $\alpha$  methyl-1, 4 pregnane-3, 20 dione 21-acetate Na salt) was obtained from the Upjohn Company of Kalamazoo, Michigan. The concentration of the methylprednisolone acetate was 40 mg/ml in a sterile aqueous suspension. The 2 and 4% solutions of L-methionine were prepared in a N-saline (W/V) sterilized by fil-

tration through a 0.20 micron plain filter unit and stored in a sterile 200 ml Erlenmeyer flask of 4° C. Preparation of stomach tissue for analysis of protein by the Biuret Method was carried out in accordance with the techniques of Colowick and Kaplan,<sup>5</sup> and measurement of the incorporation of  $^{35}\text{S}$  in trichloroacetic acid precipitated protein from gastric tissue was carried out in accordance with the methods of Mans and Novelli.<sup>6</sup> Preparation and analysis of gastric mucin for the presence of acid mucopolysaccharides were carried out by the cellulose acetate strip methods described by Kondo *et al*<sup>7,8</sup> and Buonassisi.<sup>9</sup> Stomach tissue was quantitatively analyzed for  $\beta$ -glucuronidase by the methods described by Fishman.<sup>10</sup>

The animals were caged individually upon receipt and observed for a number of days until confirmed to be healthy as noted by general appearance and until mature weights (300-400 Gm) were reached (2/14/75). The nineteen rats were then divided into four groups of four each and a fifth group of three animals. For a five-day pre-fasting, prestress period, all animals were maintained on Purina® Rat Chow containing 0.43% methionine. During this period, the average daily consumption of food and water per animal was 20-25 Gm and 5-10 ml, respectively.

During a seven day fasting period, rats in the three groups that received methylprednisolone acetate were injected in the hindquarter muscle with 6 mg (0.15 ml) of the suspension (40 mg/ml). These animals also received by intraperitoneal injection on each of the seven consecutive days 2.0 ml of either N-saline, 2% L-methionine, or 4% L-methionine. The fourth group of four animals were non-fasting normal controls and were maintained on an ad libitum diet throughout. The fifth group of three animals were fasted but did not receive steroid therapy.

Two animals in each of the first four groups received intraperitoneally a pulse of 10  $\mu\text{Ci}$  of  $^{35}\text{S}$  methionine in 1 ml of N-saline twenty-four hours prior to sacrifice and the other two animals received an intraperitoneal pulse of 10  $\mu\text{Ci}$  of  $^{35}\text{S}$  methionine in 1 ml of N-saline six hours prior to sacrifice. The animals were sacrificed by  $\text{CO}_2$  inhalation, the stomachs removed, ulcers in the glandular stomach were counted and measured, and the gastric mucosa was separated from remainder of stomach wall by blunt and sharp dissection by means of stripping with handle of scalpel and occasional use of sharp scissors. Biochemical analyses were then performed as described. Each of three additional ani-

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$\pm$ One Fishman Unit will liberate 1.0 mg of phenolphthalein from phenolphthalein glucuronide per hr. at pH of 5.0 at 37°C.

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mals in the fifth group was pulsed six hours prior to sacrifice.

TABLE 1

WEIGHT LOSS AND GASTRIC ULCERATION IN THE GLANDULAR STOMACH OF THE FASTING WHITE RAT WITHOUT METHYLPREDNISOLONE				
Group		I.P.* N-saline	I.P. 2% Methionine	I.P. 4% Methionine
No. of animals		1	1	1
Initial wt. (Gm)	2/14/75	328.5	356.5	315.0
	2/19/75	354.0	386.5	329.5
Weight loss (Gm)	2/19/75	93.5	106.5	83.0
	to 2/26/75			
Weight loss (%)	2/26/75	26.4	27.6	25.2
Number of Glandular Ulcers	2/26/76	0	0	0

\*Intraperitoneal

TABLE 2

WEIGHT LOSS AND GASTRIC ULCERATION IN THE GLANDULAR STOMACH OF THE FASTING WHITE RAT WITH METHYLPREDNISOLONE				
Group		I.P.* N-saline	I.P. 2% Methionine	I.P. 4% Methionine
No. of animals		4	4	4
Initial wt. (Gm)		334.5	327.6	338.4
(Wt. at start of experiment) (gm)		360.6	347.1	348.5
Average wt. loss (Gm) (After 7 day fast)		145.9	139.5	140.1
Average wt. loss (%)		40.4	40.2	40.2
Number of Glandular Ulcers		25	29	18

\*Intraperitoneal

TABLE 3

UPTAKE OF <sup>35</sup> S-METHIONINE BY GASTRIC TISSUE IN THE FASTING WHITE RATS (NO STEROIDS)				
Group		I.P.* N-saline	I.P. 2% Methionine	I.P. 4% Methionine
Administration of <sup>35</sup> S	6 hour pulse	6 hour pulse	6 hour pulse	6 hour pulse
No. of animals		1	1	1
Specific activity** protein of stomach wall		220±18***	355±17	361±12
Specific activity protein in mucosa		320±8	250±21	296±10

\*Intraperitoneal

\*\*Specific activity (Counts/min/mg protein)

\*\*\*Determinations done in triplicate

## RESULTS

The animals which were fasted and did not receive methylprednisolone acetate (Table 1) showed a weight loss of 25-27% of their body weight and the gastric mucosa showed no evidence of ulceration. In contrast, animals which received methylprednisolone acetate sustained an average weight loss of about 40%, and inspection of their glandular stomachs showed extensive acute ulceration (Table 2). A study of the <sup>35</sup>S uptake in the protein of the whole stomach and the gastric mucosa of fasting animals which did not receive prednisolone and were given a pulse of <sup>35</sup>S methionine six hours prior to sacrifice showed a specific activity (c/min/mg of protein) of 220-361 (Table 3). This was in contrast with a consistently lower average specific activity of 91-231 counts/min/mg of protein of eight animals receiving either I.P. N-saline or I.P. 2% methionine and steroids during the fasting period and that were pulsed with <sup>35</sup>S methionine either six or twenty-four hours prior to the sacrifice (Table 4). On the other hand, in the four animals that received 4% methionine, the average specific activity of the gastric mucosa and glandular stomach was higher than in either the N-saline or the 2% methionine group and was within the range of the animals that did not receive methylprednisolone.

The incorporation of <sup>35</sup>S in stomach tissue in a group of four normal nonfasting untreated animals was also studied. The specific activities of protein from both glandular stomach and mucosa in these control animals were considerably lower than was found in the treated groups (Table 4 and 5). Two animals in this group were pulsed with <sup>35</sup>S methionine for six hours and two were pulsed for twenty-four hours, but the specific activities were not found to differ for these two different time periods.

Protein levels of both stomach wall and mucosa in the nineteen animals ranged from 0.08 to 0.16 mg of tissue with an average of 0.12 mg. This unexplained variation was noted in all groups.

Electrophoretic separation of acid mucopolysaccharides by means of the cellulose acetate strip technique revealed that only a very small fraction of the labeled sulfur had passed through into gastric mucin. For this determination loose mucin was

TABLE 4

UPTAKE OF <sup>35</sup> S-METHIONINE BY GASTRIC TISSUE IN THE FASTING WHITE RAT WITH STEROID ULCERATIONS							
Group	I.P. N-saline		I.P. 2% Methionine		I.P. 4% Methionine		
Administration of <sup>35</sup> S*	6 hrs.	24 hrs.	6 hrs.	24 hrs.	6 hrs.	24 hrs.	
No. of animals	2	2	2	2	2	2	
Counts/min/mg protein of stomach wall	174	122	94	94	316	376	
	91	130	166	165	106	243	
Average values	129±54.7		130±41.3		260±81.2		
Counts/min/mg protein of gastric mucosa	140	166	174	147	521	155	
	231	179	141	138	270	238	
Average values	179±36.5		150±16.5		296±157.6		

\*<sup>35</sup>S-Methionine was administered on the last day of the experiment either 6 or 24 hours prior to sacrifice.

TABLE 5

UPTAKE OF <sup>35</sup> S-METHIONINE BY GASTRIC TISSUE IN THE NON FASTING NORMAL RAT	
No. of animals	4
Administration of <sup>35</sup> S	6 hour pulse 2 animals 24 hour pulse 2 animals
Specific activity* of protein in stomach wall (average values)	91 ± 12.3
Specific activity* of protein in mucosa (average values)	104 ± 12.5

\*Specific activity 4 Counts/min/mg protein

TABLE 6

**β-GLUCURONIDASE ACTIVITY IN THE STOMACH WALL OF THE FASTING AND NON FASTING WHITE RAT WITH AND WITHOUT PRIOR THERAPY USING ULCEROGENIC DOSES OF METHYLPREDNISOLONE**

Group	Fasting and Steroids I.P.* N-Saline	Fasting and Steroids I.P. 2% Methionine	Fasting and Steroids I.P. 4% Methionine	Non Fasting Normal
No. of Animals	4	4	4	4
Units/mg Protein** Average Values	11	8	3	15
Range	6-18	1-13	1-9	1-21

\*Intraperitoneal

\*\*Enzyme Activity is Expressed in Fishman Units  
(mg. of Phenolphthalein Liberated/Hr.)

TABLE 7

**β-GLUCURONIDASE ACTIVITY IN THE STOMACH WALL OF THE FASTING WHITE RAT WITHOUT METHYLPREDNISOLONE THERAPY**

Group	I.P.* N-Saline	I.P. 2% Methionine	I.P. 4% Methionine
No. of Animals	1	1	1
Units/mg Protein**	15	13	4

\*Intraperitoneal

\*\*Enzyme Activity is Expressed in Fishman Units  
(mg. of Phenolphthalein Liberated/Hr.)

scraped away gently from gastric mucosa with the handle of a scalpel. Isolated bands when tested for radioactivity in the liquid scintillation counter showed no increase in counts above background.

Finally, analysis of β-glucuronidase activity in the stomach wall of the animals on the various regimens showed a wide range of values (Tables 6 and 7). The nonfasting animals showed the highest β-glucuronidase activity and the 4% methionine fasting steroid treated animals the lowest level of activity. It was observed that 4% methionine depressed β-glucuronidase regardless of whether the animals were fasting or nonfasting, or whether they had received or had not received methylprednisolone.

## DISCUSSION

For more than 100 years, a diminished resistance of the gastroduodenal mucosa to autodigestion has been believed to be of major importance in the etiology of peptic ulcer. Beaumont, Bernard, Harley and Schiff were among those in the 19th century that pointed out that both gastroduodenal epithelium and gastroduodenal mucus were important mechanisms

by which the animal protected itself against the harmful effects of acid pepsin.<sup>11</sup>

In more recent years, the role of good nutrition in the preservation of body integrity has been increasingly emphasized. The stressed animal or the animal that has received large doses of hydroxycorticosteroids has been found to excrete large quantities of sulfur as well as nitrogen, calcium, potassium and other substances as the result of catabolic processes. It is logical therefore, that adrenal steroids and injury or stress of any kind will be poorly tolerated by nutritionally depleted animals. It has been hypothesized that the increased susceptibility of the

stressed and depleted animals to peptic ulceration is partly related to a deficiency of sulfated mucosubstances.<sup>12</sup> Current understanding is that the effect of burns, trauma, and febrile illnesses is, in part, a stimulation of metabolic processes of which catabolism is only one phase. It is believed that following injury there is a redistribution of essential substances to make way for regrowth and recovery. There is nitrogen loss and aminoaciduria (for example taurine),<sup>13</sup> but there is also an increase in amino acids and total nitrogen within the liver, as well as an increase of enzyme function. Furthermore, there is evidence of a redistribution of essential materials to other areas of need, such as leukocyte production, wound repair and increased production of serum albumin and serum globulin. The importance of sulfur amino acids in the healing process following burns and other severe injuries has been emphasized by Cuthbertson, Croft and Peters, Localio, Williamson and others.<sup>14,12</sup> In addition, if insufficient calories are provided the stressed animal, deamination of amino acids takes place for caloric needs.

The need for nutritional supplementation with specific amino acids is poorly understood, and there has been little study of specific needs in the animal that is injured and diseased. In the depleted animal, it is difficult to show a deficiency of methionine per se. Methionine levels in blood and tissue have been shown to remain constant despite a lack of sulfur amino acids in the diet. Plasma levels of cystine, however, become greatly reduced.<sup>15</sup> A systemic need for methionine itself apparently results in the maintenance of relatively normal tissue levels.

Among the well recognized major functions of methionine are those of (a) its essential contribution to protein synthesis, (b) its role in the production of S-adenosyl methionine (the primary methyl group donor) and (c) its part in the conversion via the trans-sulfuration pathway to cystathionine, cysteine and other derivatives of cysteine.<sup>16</sup> It is quite likely that these needs for methionine are competitive. It is also quite possible that the need for cysteine or cystine as a sulfur donor for the sulfation of acid mucopolysaccharides for the gastrointestinal tract, as well as for mesenchymal tissue, is also competitive. The repair of extensive tissue loss, for example, may require large quantities of sulfur-containing amino acids leaving little sulfur to contribute to replenishment of mucosa or little sulfur to contribute to sulfation of acid mucopolysaccharides. Gastric mucosa is highly anabolic and will rapidly incorporate methionine. It is logical that the depleted animal will have even greater requirement for essential amino acids and will incorporate methionine at an even greater rate. It is not known, however, whether the stressed animal or the animal receiving large amounts of adrenal steroids is able to utilize beneficially free methionine or free inorganic sulfate in significant amounts.

Many observers have indicated that adrenal steroids have deleterious effects on the metabolism of the gastric mucosa, as well as on the metabolism of mesenchymal tissues. These effects may be due to enhancement of metabolic processes or to poorly understood inhibitory effects. Inhibition of the synthesis of chondroitin sulfate in cartilage by cortisone was reported by Layton<sup>17</sup> in 1951 and the subject of endocrine control of connective tissue was reviewed in 1959.<sup>18</sup> A reduction in gastric mucin was observed histologically following the administration of cortisone and hydrocortisone by Baker and Bridgeman.<sup>19</sup> A decrease in gastric mucous production was observed by Hirschowitz *et al* in patients receiving adrenocorticotropin.<sup>20</sup> Denko demonstrated that cortisone would inhibit the incorporation of radioactive sulfur into gastric mucin in 1958,<sup>21</sup> and Halme and coworkers<sup>22</sup> found that cortisone acetate reduced conjugation and probably reduced synthesis of glucuronic acid in duodenal mucosa. Menguy and Masters, in 1963, found that the administration of cortisone to dogs prepared with denervated gastric pouches caused a substantial decrease in the rate of mucus secretion by these pouches.<sup>23</sup> Goksen and Hardy,<sup>24</sup> and Sun and Spicer<sup>25,26</sup> also found evidence of a decreased production of mucus as a result of cortisone administration. Kowalewski, however, observed that whereas the radioactivity of the sulfated mucopolysaccharides was reduced in the cortisone-treated animal, anabolic hormones would prevent this change.<sup>27</sup>

Other studies have indicated that whereas the effect of adrenal steroids over a short period of time may or may not be inhibitory, the chronic adminis-

tration of either small or large doses over days and weeks may actually speed up metabolic processes, thereby resulting in a marked increase in the synthesis of gastric mucopolysaccharides. Belanger<sup>28</sup> injected a weak solution of sulfuric acid into 10 day old rats and found that a tracer dose of <sup>35</sup>S could be localized autoradiographically in the mucous neck cells of the stomach. These autoradiographical findings have been confirmed by Bostrom and Odeblad<sup>29</sup> and by Jennings and Florey,<sup>30</sup> who found that the strongest radioactivity appeared from one to three hours after the injection of sulfate and then fell off rapidly so that little activity in the specimen was present 12 to 24 hours after injection. No activity was found in the superficial epithelial cells, but intense activity was present in the bases of the foveolae and streams of radioactive mucin were seen pouring toward the mucosal surface. Following the intravenous injection of Na<sub>2</sub><sup>35</sup>SO<sub>4</sub>, Kent and coworkers<sup>31</sup> found that <sup>35</sup>S, largely in the form of an ester sulfate, would be incorporated into gastroduodenal mucin. They thought it probable that sodium sulfate passed through the duodenal mucosa with water and that under these conditions would "probably be freely available to the cells that are synthesizing muco-substances." Only an estimated 0.05% of the administered intake became incorporated in the duodenal mucin. In their experiments they found that whereas less <sup>35</sup>SO<sub>2</sub>-2 is secreted in the mucin under the influence of cortisone, cortisone had no apparent effect on the rate of incorporation of <sup>35</sup>S methionine into the duodenal mucous secretion. Lev *et al*<sup>32</sup> in a histochemical study of the canine stomach found mucous cell hyperplasia and autoradiographical evidence of increased mucus synthesis as a consequence of prednisone administration. Bremen *et al* made the same observation following the chronic administration of cortisone acetate and found a quantitative increase in the production of total and acidic glycoproteins in the dog. An increased secretion of sulfated mucosubstances in the fundic crypt of dogs on long term cortisone acetate therapy was also found by Willems, Gerard and Verbeustel by histochemical and autoradiographic techniques.<sup>34</sup>

In our studies, although the fasting animal was found to incorporate two to three times as much <sup>35</sup>S methionine or its degradation products with gastric tissue as did the normal control animal, the intramuscular administration of methylprednisolone was found to reduce this rate of incorporation substantially. Furthermore, the daily intraperitoneal administration of L-methionine in a 4% solution appeared to permit the incorporation of greater amounts of the tracer dose of <sup>35</sup>S methionine, and these amounts were in the same range as were taken up by the animals that did not receive methylprednisolone. This finding suggests that intraperitoneally administered methionine counteracts or compensates for one of the deleterious effects of adrenal steroids in the fasting animal. However, it is also

possible that intraperitoneal free L-methionine at this concentration may interfere with the metabolism of hepatic and other tissues, as the toxicity of excessive doses of methionine has been well known for many years.

Earle and Kendall in 1942<sup>35</sup> described some of the harmful effects of excessive methionine administration and other changes have since been described, such as an elevation of histidine in plasma and liver, low tissue levels of ornithine and arginine, and tissue deficiencies of glycine and serine. Harmful effects of these amino-acid imbalances have been described, such as alteration in the quality of hepatic enzymes and retardation of normal growth. Four percent added methionine has been said to interfere with normal growth, but 2% supplementation has permitted growth in young force-fed rats.<sup>15</sup>

In our experiments, methionine did not in a time span (6-24 hours) contribute significantly to the sulfation of gastric mucopolysaccharides of animals that had or had not been fasting, and animals that had or had not received methylprednisolone, as determined by cellulose acetate strip electrophoresis. We also found that L-methionine administered intraperitoneally contributed strongly to protein metabolism of gastric tissue, as little or no change in radioactive specific activity counts from gastric tissue were noted over a period of from 6 to 24 hours. These results confirm the findings of Kent *et al* who in 1956 found that <sup>35</sup>S methionine administered intravenously was strongly incorporated into gastric mucosa and into mucosubstances and could be identified as <sup>35</sup>S methionine after acidic hydrolysis of mucoprotein and chromatography of the hydrolysate. As such, it was one of 12 identified amino acids. There was no evidence of its conversion into sulfate in this relatively acute experiment in the rabbit. In addition, unlike <sup>35</sup>SO<sub>4</sub>-2 which was rapidly lost from the blood stream, <sup>35</sup>S methionine was retained for up to ten days, suggesting that it had become distributed throughout the body. This suggested that methionine is not an immediate precursor of sulfate in the synthesis of gastric mucosubstances. However, it does not preclude the probability that breakdown products of organic sulfur-containing amino acids contribute to the eventual sulfation of mucopolysaccharides through the phosphoadenosine-phosphosulfate pathway (P.A.P.S.). In conclusion, it is believed that free L-methionine given by mouth (or intraperitoneally, as in our experiment) is taken up by the portal system and will contribute to the synthesis of gastric mucosa. It will also eventually contribute to the available pool of sulfur for use in the sulfation of gastric mucopolysaccharides. Partial confirmation of this was obtained by study of microscopic sections of glandular stomach of the fasted, stressed and L-methionine-treated rat which were found more strongly stained with alcian blue than were the stomachs of a normal control or the stomach of a

fasted, stressed animal that received only intraperitoneal saline.

## SUMMARY

The effects of stress, severe injury or adrenal hydroxycorticosteroids on the gastrointestinal mucosa remain controversial. Some observers have noted an increased synthesis and excretion of acid, pepsin and sulfated mucosubstances as the result of the chronic administration of adrenal corticosteroids. Others have noted a decreased synthesis and sulfation of gastrointestinal mucopolysaccharides under similar circumstances. It is possible that these apparently contradictory observations may be related to differences in the severity and duration of the stress and in the dosage of the administered adrenal corticosteroids. It is believed that any stress or injury that is sufficiently severe and prolonged will result in a preponderance of catabolism, and that inhibition of synthesis of gastroduodenal secretory epithelium and decrease in synthesis and sulfation of gastrointestinal mucopolysaccharides are associated phenomena. The injurious effects of stress and injury are naturally more severe in the depleted animal. On the other hand, if stress is not overwhelmingly severe, then adaptation takes place and adrenal cortical steroids, perhaps through permissive action, facilitate increased metabolic activity including the increased synthesis of sulfated mucopolysaccharides. If the effect of adrenal steroids is, in this regard, one of hypermetabolism, it is conceivable that ulceration could develop in areas of the stomach and duodenum where there is temporary exhaustion of secretory epithelial cells. It is quite obvious that no cell or tissue can be expected to secrete continuously or to live forever. This idea was expressed years ago<sup>12,3</sup> and it was recently restated by Willems *et al* after they had observed the enhanced secretion of gastric mucopolysaccharides as the result of long term administration of cortisone acetate.

In this experiment we have confirmed the findings of Kent *et al* that <sup>35</sup>S methionine becomes strongly incorporated into stomach tissue but contributes very little to the immediate sulfation of acid mucopolysaccharides. We also found that the degree of this incorporation is greatly diminished in the steroid-treated animal. Finally, we found that the administration of large amounts of L-methionine appears to counteract the deleterious effects of methylprednisolone on the glandular mucosa of the fasting rat.

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*Continued on Page 243*

# Hypoglycemia Due to Pathology of the Exocrine Pancreas and the Peripancreatic Area\*

A Clinicopathologic Survey of Veterans Administration Hospital Patients

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## ABSTRACT

A nation-wide search of U. S. Veterans Administration hospital records covering a 10-year period yielded clinical summaries and autopsy findings of 98 patients with persistent hypoglycemia. In 50 patients (51%), the hypoglycemia was associated either with diffuse pancreatitis or with localized pathological findings in the exocrine pancreas or in the peripancreatic region. The hypoglycemia usually was severe and often fatal. It is postulated that these lesions interfere with the intricate neurogenic control of hormone secretion and glucose homeostasis by an ectopic stimulation of autonomous nerve fibers within the pancreas or in the peripancreatic area.

While in the course of acute or chronic pancreatitis hyperglycemia and pancreatic diabetes are frequently seen, hypoglycemia is a fairly rare occurrence. A number of publications concerning the syndrome of pancreatitis associated with severe hypoglycemia have appeared, particularly in the European literature. However, the syndrome has not received much attention in this country. French authors called this entity, "pancréatite chronique hypoglycémique."<sup>1</sup> In a review of the world literature for the years 1934-1958, I compiled 43 cases of hypoglycemia associated not only with pancreatitis but also with other pathological changes in the exocrine pancreas as well as in the peripancreatic area and the biliary tract.<sup>2</sup> Of particular interest were two cases of traumatic, hemorrhagic pancreatitis in which rather severe hypoglycemia appeared within exactly the same time interval, i.e., three months after the accident. A clinicopathologic survey among Veterans Administration patients hospitalized in the years 1950 through 1958 yielded 10 cases of hypoglycemia in which postmortem evidence of pancreatic and peripancreatic lesions or disease in the biliary tract was documented. I proposed at that time that these pathological changes caused hypoglycemia by abnormal stimulation of the autonomous nervous system.<sup>3</sup> In order to aug-

ment the previous study, this more extensive survey of Veterans Administration patients was carried out.

## SUBJECTS AND METHODS

With the cooperation of the Medical Administration Service of the Department of Medicine and Surgery, U. S. Veterans Administration, Washington, D. C., 170 VA Hospitals were requested to furnish clinical summaries and autopsy reports of all patients with hypoglycemia who had died and in whom autopsy findings were available during the 10-year period from 1963 through 1972. Patients were regarded as hypoglycemic if the blood sugar was below 45 mg/dl on more than one occasion. Their age ranged from 29 to 80 years with an average age of 52 years. Bronchopneumonia, pulmonary embolism and arteriosclerotic heart disease were the most frequent causes of death.

## RESULTS

Inasmuch as only cases with autopsy findings were included in this study, it does not constitute a true statistical evaluation of the incidence of hypoglycemia. Neither should it be construed to give an accurate distribution of hypoglycemia among the different categories of pancreatic or peripancreatic disease mentioned in this paper.

The survey yielded 98 cases of severe hypoglycemia from various causes. After review of the clinical, laboratory and pathological findings they were divided into two major categories as shown in Tables 1 and 2. Table 1 comprises 50 patients with the syndrome that is the subject of this paper, namely, hypoglycemia secondary to pathology of the exocrine pancreas or the peripancreatic region or of the biliary tract (cholangitis or cholelithiasis). Table 2 lists patients with severe hypoglycemia due to other pathologic processes or with hypoglycemia of uncertain etiology such as various combinations of malnutrition, alcoholism, liver failure, severe infection and sepsis. They are reported only for the sake of completeness and will not be considered further as they are not pertinent to the objective of this paper.

In many cases hypoglycemia was profound and often persistent until death. This fact is best illus-

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TABLE 1

**HYPOLYCEMIA ASSOCIATED WITH PATHOLOGY OF THE EXOCRINE PANCREAS OR OF THE PERIPANCREATIC REGION**

I. Diffuse inflammation of pancreas	26
1. Acute pancreatitis	6
2. Chronic pancreatitis	9
3. Calcifying pancreatitis	11
II. Non-inflammatory lesions of pancreas	9
1. Primary tumor other than insulinoma	1
2. Metastatic tumor	5
3. Anthracotic lymphnodes of unknown etiology	1
4. Hemochromatosis	1
5. Polycystic disease of pancreatic ducts	1
III. Lesions in the peripancreatic area	15
1. Metastatic neoplastic infiltration	1
2. Myelocytic infiltration	1
3. Lymphadenopathy due to Hodgkin's disease	4
4. Lipogranulomatous lymphadenitis of unknown etiology	1
5. Peripancreatic hemorrhage secondary to anticoagulation	1
6. Penetrating gastric ulcer	1
7. Cholangitis or cholelithiasis	6
Total number of cases	50

TABLE 2

**HYPOLYCEMIA ASSOCIATED WITH OTHER MISCELLANEOUS PATHOLOGICAL CONDITIONS**

1. Insulinoma	2
2. Hepatoma	6
3. Retroperitoneal tumor	6
a. Schwannoma	1
b. Mesothelioma	1
c. Fibrosarcoma	3
d. Mesenchymoma	1
4. Bronchogenic carcinoma	3
5. Addison's disease	3
6. Various combinations of malnutrition, alcoholism and liver failure	17
7. Terminal states	6
8. Severe infection and sepsis	4
9. Chlorpropamide medication in renal failure	1
Total number of cases	48

trated by quoting passages from some of the clinical summaries:

"Constant i.v. infusion of glucose solution was required to prevent hypoglycemic shock."

"Continuous i.v. infusion of 20% dextrose solution was required to keep the blood sugar at 65 mg/dl. Patient received 300 gm dextrose a day."

"Massive glucose infusions had to be continued, but we were unable to keep up with the patient's vast demands. The insulin assay was normal."

"The blood sugar remained at 18 mg/dl after i.v. infusion of more than 200 gm dextrose."

"Severe, prolonged hypoglycemia occurred after administration of 5 units NPH insulin, requiring 140 gm dextrose i.v."

In several instances, blood sugar values were below measurable levels. Twenty patients, i.e., 40% of all patients listed in Table 1, developed severe hypoglycemia, with or without brain damage, that was refractory to treatment and persisted until death (Table 3). Ten patients with initial diabetes mellitus

TABLE 3

**INCIDENCE OF IRREVERSIBLE HYPOLYCEMIA**

1. Acute pancreatitis	3
2. Chronic pancreatitis	5
3. Intrapancreatic metastatic tumor	1
4. Peripancreatic lesions	7
Total number of cases	16

TABLE 4

**EMERGENCY OF SPONTANEOUS HYPOLYCEMIA IN PREVIOUSLY DIABETIC PATIENTS**

1. Acute pancreatitis	2
2. Chronic pancreatitis	3
3. Calcifying pancreatitis	4
4. Peripancreatic metastatic tumor	1
Total number of cases	10

exhibited increasing sensitivity to insulin and finally became hypoglycemic, often to a severe degree, without further use of insulin (Table 4). A case of peripancreatic hemorrhage is of special interest as it is very similar to two cases of traumatic pancreatitis with severe hypoglycemia mentioned above. Plasma insulin assays were reported in a minority of cases only, but, whenever done, did not show an elevated insulin level and several revealed no insulin at all. Unfortunately, no glucagon assays were mentioned in any of the clinical summaries, possibly because no accurate method of plasma glucagon determination was generally available at the time these patients were hospitalized (1963-1972).

**REVIEW OF PERTINENT ANATOMICAL AND EXPERIMENTAL STUDIES**

The pancreas is surrounded by a dense network of autonomous nerve fibers arising from the left iliac plexus and the right (dorsal) vagal trunk. These nerve fibers penetrate deep into the inter- and intralobular spaces and are in close contact with the alpha and beta cells and their capillary blood supply. Cell complexes consisting of an intimate association of nervous and epithelial cells are situated in the inter- and intralobular septa. Endocrine cells, containing specific granules, have been detected in acinar ductules. These structures most likely represent neuro- and chemoreceptors that govern glucagon and insulin secretion.<sup>4</sup> Furthermore, direct interaction between the two hormones is facilitated by the existence of gap junctions between alpha and beta cells as demonstrated by electron microscopy.<sup>5</sup>

The great importance of glucagon for the maintenance of euglycemia was demonstrated by the appearance of severe, often fatal, hypoglycemia following partial or total pancreatectomy in lizards, ducks and other birds.<sup>6</sup> Grey, *et al* produced a specific, isolated deficiency of glucagon associated with hypoglycemia in fasted rats by intravenous injections of a high-titer glucagon antiserum.<sup>7</sup>

The neurogenic regulation of carbohydrate metabolism has been the subject of numerous studies. Because of space limitations, only a few will

be considered here. In man, injection of atropine produced a significant fall in fasting glucagon and reduced the normal rise of glucagon after arginine infusion by 33%. The glucagon response to insulin produced hypoglycemia in 10 patients with truncal vagotomy was significantly less than that in a matched group of patients with selective vagotomy.<sup>8</sup> Propranolol, a beta-adrenergic blocking agent, has been found to depress glucagon secretion. Wray, *et al* published the occurrence of severe hypoglycemia in a 71-year-old male who had been given propranolol for relief of angina pectoris over a period of several years.<sup>9</sup> Propranolol also has been used in the management of juvenile diabetes in order to dampen glucagon secretion.

In baboons and dogs, electric stimulation of the dorsal (right) vagal trunk caused a considerable increase in insulin secretion which, however, was not followed by hypoglycemia.<sup>10,11</sup> Of special interest are the experiments by Loubatières and his co-workers<sup>12</sup> who reported that increased pressure in the pancreatic duct in anesthetized dogs caused a drop in blood sugar level. The authors considered the possibility of either a direct excitation of the islands or a reflex action of the islands in response to a stimulation of vegetative nerve fibers. This assumption was reinforced by experiments on the cat pancreas during which numerical changes of alpha and beta cells of the islands of Langerhans could be produced by suitable stimulation of sympathetic and parasympathetic nerve fibers.

#### DISCUSSION

A similar mechanism may be responsible for the severe hypoglycemia observed in our patients. In view of the close proximity of exocrine and endocrine structures within the pancreas, acute or chronic pancreatitis can easily derange the architectural integrity of the islands. Furthermore, dilatation of the pancreatic ductules due to obstruction by calcifications and tumor as well as inflammatory changes involving the exocrine pancreas or the parapancreatic area may lead to excitation of the autonomous nerve fibers that are abundantly present within the pancreas and in the surrounding tissue. This in turn may result in an altered functional sensitivity and responsiveness of alpha and beta cells and thus upset the orderly maintenance of homeostasis by the autonomous nervous system. This is especially true in view of the discovery of direct morphological communications between alpha and beta cells that has led to the concept of the islet being one mass of cells working in unison as a multihormonal unit, whereby the proper alpha/beta cell ratio seems to be physiologically more important than the absolute number of either cell type.<sup>13,14</sup> The free interplay between alpha and beta cells and thus between glucagon and insulin under the overall control by chemo- and neuroreceptors can be considered the *sine qua non* for a prompt response to constantly changing metabolic requirements.

The appearance of hypoglycemia in the course of pancreatic disease is a fairly rare phenomenon. In certain patients, the frequently present hyperglycemia is then followed by a gradual amelioration of the diabetes and eventually by a marked hypoglycemia that may become irreversible and fatal. In the past, this development was often attributed to an overcompensating regeneration of beta cells resulting in hyperinsulinism. However, this theory has been generally abandoned. In our survey, emergence of pronounced hypoglycemia was seen in ten previously diabetic patients even after insulin administration had been discontinued (Table 4).

During recent years, Joffe and co-workers reported the occurrence of severe hypoglycemia in eight patients with chronic calcifying pancreatitis.<sup>15</sup> They suspected hypoglucagonemia to be the cause of the hypoglycemia. Bank, *et al* detected true hypoglucagonemia in 16% of patients with chronic pancreatitis. Stimulated growth hormone secretion was deficient also. They observed that hypoglycemia when it occurred was severe and resistant to therapy and considered hypoglycemic coma an important cause of death in calcific pancreatitis.<sup>16</sup> Donowitz, *et al* found that patients with *acute* pancreatitis had a markedly increased glucagon response to alanine while those with repeated bouts of pancreatitis showed a diminished response with each successive attack until in *chronic* pancreatitis a complete lack of glucagon secretion after alanine stimulation became evident. They attributed this development to a gradual loss of alpha cell responsiveness resulting in hypoglucagonemia.<sup>17</sup> A similarly impaired response of glucagon secretion to arginine was observed also in cystic fibrosis of the pancreas.<sup>18</sup>

The present survey yielded 98 cases of severe hypoglycemia. In 50 patients, i.e., in 51% of the total number, the hypoglycemia was associated with pathologic findings in the exocrine pancreas and in the peripancreatic region. This fact points to an important relationship between these lesions and the severe impairment of carbohydrate metabolism seen in these patients. The incidence of hypoglycemia associated with different disease entities is listed in Table 1. The clinical picture of our patients with acute and chronic, especially calcifying, pancreatitis (Group I, Table 1) and severe hypoglycemia is very similar to that reported by other investigators as cited above. It is worthy of note that the incidence of intractable hypoglycemia amounted to 47% of the patients with parapancreatic lesions and only 26% of those with intrapancreatic disease (Table 3). Conversely, hypoglycemia occurred in about the same number of patients with diffuse, inflammatory pancreatic disease (Group I, Table 1) as in patients with more localized intra- and extrapancreatic lesions (Groups II and III, Table 1).

One can only hypothesize as to the nature of the hormonal imbalance responsible for the hypoglycemia in our patients as no glucagon assays were

done. However, in view of the hypoglucagonemia reported by other investigators in their patients with pancreatitis and severe hypoglycemia (see above) one might assume that in our cases, too, the hypoglycemia was due to a relative or absolute glucagon deficiency. The severity of the hypoglycemic state that often proved refractory to treatment also argues for hypoglucagonemia. Hypoglycemia due to lack of glucagon has been found to be especially severe because even ample glycogen stores in the liver cannot be mobilized without the glycogenolytic action of glucagon.<sup>19</sup>

A diffuse pathologic process in the exocrine pancreas may cause strangulation, isolation or destruction of the islands. This may be accompanied by a change of the physiological glucagon/insulin ratio due to either an actual loss of alpha cells or a diminution of their functional responsiveness. However, mere morphological changes of the islets cannot explain the occurrence of severe hypoglycemia in patients with fairly localized lesions in the pancreas or in the parapancreatic area (Groups II and III, Table 1) as only a limited number of islands or none at all may be affected. It seems appropriate to assume that these lesions upset normal glucose homeostasis by an ectopic stimulation of autonomous nerve fibers within the pancreas and in the peripancreatic region.

The above premise is reinforced by several clinical reports of complete alleviation of severe hypoglycemia following denervation of the pancreas in the course of a negative exploration of the organ for the possible presence of an insulinoma without removal of any pancreatic tissue. Schen published the case of a 50-year-old man with cholelithiasis and severe hypoglycemia manifested by repeated episodes of unconsciousness with very low blood sugar levels.<sup>20</sup> A thorough exploration of the pancreas was carried out but no insulinoma was found and the organ was left intact. After the operation, the patient's symptoms were relieved completely. A glucose tolerance test two years later was normal. The author suggested that the separation of the pancreas from the adjacent tissues with interruption of the neural pathways was responsible for the patient's complete recovery. He cited a number of similar cases from the medical literature where severe hypoglycemia ceased entirely following either denervation of the pancreas or bilateral vagotomy.

### CONCLUSION

This paper directs attention to the occasional occurrence of severe hypoglycemia in patients with pancreatitis or other pathologic processes within the pancreas as well as in the parapancreatic area. Reiterating my previous hypothesis as to the etiology of this syndrome,<sup>3</sup> I wish to suggest that pancreatic or parapancreatic lesions may upset the neurogenic control of hormone secretion and cause

hypoglycemia by an ectopic stimulation of autonomic nerve fibers within the pancreas or in the parapancreatic region. The exact nature of this hormonal imbalance cannot be deduced from the present study because relatively few assays of plasma insulin and none of plasma glucagon were recorded in the clinical summaries. Nevertheless, the severity and frequent intractability of the hypoglycemic state seen in our patients argues for the presence of absolute or relative hypoglucagonemia rather than of hyperinsulinism since plasma insulin assays did not show an increased insulin level.

Although this syndrome is apparently quite rare, it should be kept in mind as a potentially dangerous complication of pancreatic and parapancreatic disease.

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## Management of the Disulfiram-Alcohol Reaction

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### ABSTRACT

Manifestations of the typical disulfiram-alcohol reaction begin within 5 to 15 minutes after alcohol ingestion in a subject pretreated with disulfiram, and generally appear in the following order: flushing and a "lobster-red" color accompanied by a sensation of warmth and diaphoresis, palpitations, dyspnea, hyperventilation, tachycardia, headache and hypotension. The hypotension may produce pallor, weakness, vertigo, nausea and vomiting. Electrocardiographic changes may also occur. Although the reaction is usually short-lived and without sequelae, severe adverse effects have been reported and at least 20 deaths have been reported.

Disulfiram inhibits at least two enzyme systems within the body: acetaldehyde dehydrogenase and dopamine-beta-hydroxylase. The typical disulfiram-alcohol reaction appears to result from the direct cardiovascular depressant effects of excessive concentrations of ethanol and acetaldehyde concurrent with norepinephrine depletion. Recommended treatment consists of supportive measures such as Trendelenberg posture, administration of oxygen, and intravenous infusion of fluid, solute, colloid, and, if needed, a pressor agent such as norepinephrine. Iron salts, ascorbic acid, antihistamines, and phenothiazines are of no established benefit.

Disulfiram (tetraethylthiuram disulfide) was first used in the management of chronic alcoholism in 1948, when it was accidentally discovered that human subjects pretreated with disulfiram experienced a characteristic, unpleasant reaction following the ingestion of small amounts of ethanol.<sup>1,2</sup> Even before this time, similar reactions had been noted in individuals exposed to ethyl alcohol and a number of other compounds, including carbon disulfide, cyanamide, tetramethylthiuram disulfide, tetraethylthiuram monosulfide and the fungus *Cop-*

*rinus atramentarius*.<sup>3</sup> The efficacy of disulfiram in the management of chronic alcoholism and the mechanism of the typical disulfiram-alcohol interaction remain uncertain.<sup>3-12</sup> The present paper reviews the proposed mechanisms of the disulfiram-alcohol interaction and discusses recommended management.

### EFFICACY OF DISULFIRAM IN THE MANAGEMENT OF ALCOHOLISM

Lundwall and Baekeland<sup>1</sup> critically reviewed the literature on disulfiram treatment of alcoholism published between 1948 and 1971, finding that almost all studies were inadequately designed. They suggested the following criteria for valid comparisons between disulfiram and other treatment methods: comprehensive and explicit objective criteria for measuring improvement; single-blind study design; appropriately matched treatment and control populations; adequate follow-up periods (at least 6 months); and statistical analysis of results. Of over 40 studies reviewed, only one met most of these requirements<sup>13</sup> and only five used control groups of any kind.<sup>13-17</sup> Reported rates of improvement in patients receiving disulfiram vary from 19% to 83%. Although the efficacy of disulfiram relative to other methods of treatment is not established, it does appear that disulfiram may be a useful adjunct in the management of some chronic alcoholics. Patients most likely to benefit are over 40 years of age, well-motivated, socially stable, not depressed, compulsive, and able to form dependent relationships.<sup>4</sup> Since such patients comprise only a minority of alcoholics, the role of disulfiram in the routine management of the chronic alcoholic remains uncertain.<sup>5</sup>

### SIGNS AND SYMPTOMS OF DISULFIRAM-ALCOHOL INTERACTION

The characteristic disulfiram-alcohol reaction usually begins within 5 to 15 minutes after alcohol ingestion in a subject pretreated with disulfiram. As little as 15 ml of alcohol can produce the reaction; a single dose of disulfiram administered 3 to 12 hours previously may also sensitize the patient.<sup>4,18</sup> Typical disulfiram reactions have been observed in several patients who either drank alcohol after the ingestion of a single disulfiram tablet or who were adminis-

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tered disulfiram while still under the influence of alcohol.

The reaction usually begins with flushing and a "lobster-red" color, initially at the top of the head, then progressing to the face, sclera and conjunctiva, upper extremities and chest. The flushing is accompanied by palpitations, dyspnea, hyperventilation, tachycardia and, occasionally, chest pain (simulating cardiac ischemia). A pounding headache is common and a fall in systolic and diastolic blood pressure is seen in almost all patients; severe cardiovascular collapse has occurred in a few cases. The hypotension may produce pallor, weakness, vertigo, nausea and vomiting. Drowsiness and sleep usually follow with eventual complete recovery within two to four hours.<sup>4,12,18</sup>

Disulfiram-alcohol reactions are also frequently accompanied by transient electrocardiographic (ECG) changes. These changes typically include flattening of the T-waves and sometimes ST-segment depression. They usually develop within 90 minutes after ethanol ingestion and only occasionally persist for longer than four hours. It is believed that the ECG changes are nonspecific consequences of tachycardia and increased cardiac work, although Raby<sup>12</sup> has proposed that hypokalemia accompanying the disulfiram-alcohol reaction may also be responsible.

Even though the disulfiram-alcohol reaction is usually short-lived and without sequelae, severe adverse effects have been reported<sup>4</sup> and at least 20 deaths have occurred.<sup>19-21</sup> A fatal episode has even been described during a "test" reaction given by a physician.<sup>22</sup> Many of the fatalities have been "unexplained"; intracranial hemorrhage has been documented, and acute myocardial infarction, cardiac arrhythmias, pulmonary edema, and cerebral edema have been speculated as the cause of death in several instances. In eight of 13 cases reviewed by Amador and Gazdar,<sup>19</sup> the disulfiram dosage appeared to be excessive as judged by current standards. The frequency of fatalities and severe side effects apparently has been diminished by the lowered dosage regimens currently recommended and by eliminating the disulfiram-alcohol test reaction.<sup>4</sup> However, at least two cases of intracranial hemorrhage have been reported in patients receiving proper dosages of the drug.<sup>20,21</sup>

Although the characteristic reaction usually lasts from two to four hours, the intensity and duration of the symptoms are directly related to the disulfiram dosage, the amount of alcohol ingested, and, to some degree, individual sensitivity.<sup>4,12,18</sup> Thus, the reaction may persist for several hours (as long as ethanol remains in the blood); additionally, symptoms following alcohol intake are generally more intense the longer the duration of prior disulfiram administration. Since disulfiram is slowly eliminated from the body,<sup>23</sup> typical reactions to the ingestion of alcohol may occur up to two weeks after disulfiram administration is discontinued.<sup>4</sup>

## MECHANISM OF DISULFIRAM-ALCOHOL INTERACTION

The mechanism of the disulfiram-alcohol reaction remains obscure. The model proposed by Nakano, Gin and Nakano probably has the greatest merit (Figure 1).<sup>8</sup>

Several studies performed shortly after the introduction of disulfiram indicated that the disulfiram-alcohol reaction was due to the accumulation of acetaldehyde in the blood. Disulfiram has been found to be a potent, competitive inhibitor of aldehyde dehydrogenase, which catalyzes the metabolism of acetaldehyde to acetyl coenzyme A. Following the administration of ethyl alcohol to animal and human subjects pretreated with disulfiram, the concentration of acetaldehyde in the blood is much higher than following the ingestion of ethanol alone. Further, the appearance and disappearance of the signs and symptoms of the disulfiram-alcohol reaction coincide with the rise and decline in acetaldehyde concentrations. Infusion of acetaldehyde into human subjects not pretreated with disulfiram reproduces many of these symptoms (hyperventilation, tachycardia, vasodilation in the face). However, additional evidence suggests that acetaldehyde accumulation is not entirely responsible for the disulfiram-alcohol reaction.<sup>4,6,8</sup>

Raby<sup>12</sup> observed that even though the concentration of acetaldehyde in the blood was always increased after disulfiram and alcohol (and was usually higher than after ethanol alone), the same high levels of acetaldehyde could occasionally be obtained after alcohol alone without producing any of the manifestations characteristic of the disulfiram-alcohol reaction. Acetaldehyde administered intravenously to dogs stimulated respiration via chemoreceptors, dilated the bronchial tree, increased arterial blood pressure and increased heart rate. Thus acetaldehyde appears to have sympathomimetic properties that are mediated through its release of stored catecholamines from both adrenal medulla and sympathetic nerve endings.<sup>4</sup> Perman<sup>3</sup> also found that acetaldehyde had sympathomimetic properties when infused intravenously into disulfiram-pretreated rabbits. The effect was much less marked when acetaldehyde was infused slowly, mimicking the clinical situation. Hypotension could not be elicited when acetaldehyde was slowly infused into unpretreated animals.

Disulfiram also inhibits dopamine-beta-hydroxylase resulting in norepinephrine depletion from sympathetic nerve endings and the adrenal medulla.<sup>9-11</sup> Vesell et al<sup>9</sup> demonstrated an alteration in dopamine metabolism secondary to disulfiram administration. Urinary concentrations of vanilmandelic acid (VMA) decreased, and concentrations of homovanillic acid (HVA) increased, in human volunteers given disulfiram. Disulfiram may render beta-hydroxylation the rate-limiting step in

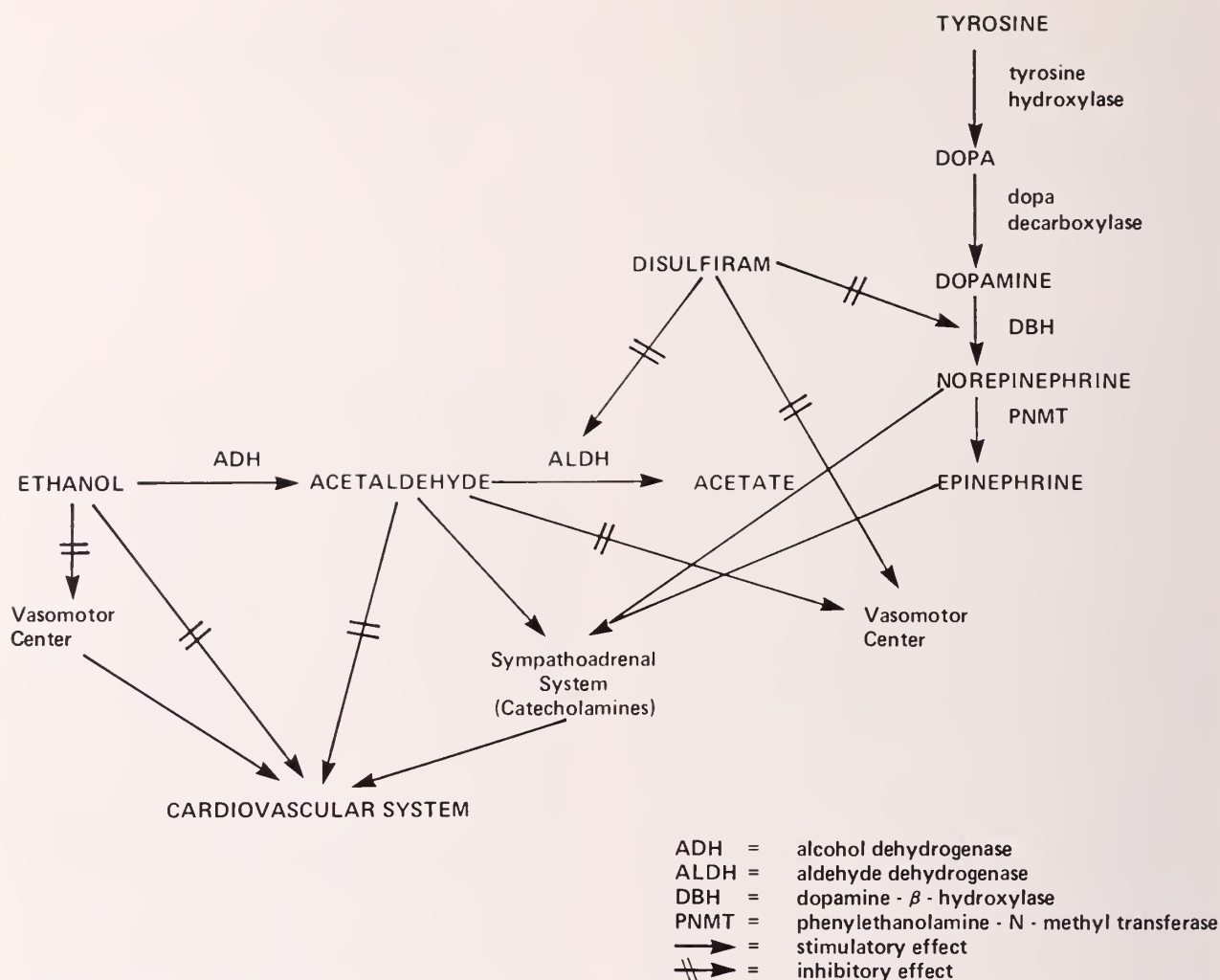


Fig. 1. Mechanism of Cardiovascular Effects of Disulfiram-Alcohol Reaction (Modified from: Nakano, J., Gin, A. C., Nakano, S. K.: Effects of disulfiram on cardiovascular responses to acetaldehyde and ethanol in dogs. *Q J Stud Alcohol* 35: 620-634, 1974.)

catecholamine synthesis, whereas tyrosine hydroxylase is normally the rate-governing enzyme.<sup>9</sup>

Nakano and associates<sup>8</sup> have contributed importantly to our understanding of the complex mechanism of the cardiovascular abnormalities seen during the disulfiram-alcohol reaction. Sudden bilateral carotid artery occlusion significantly increased heart rate and systemic arterial pressure in normal dogs; however, no such increases were observed in dogs pretreated with disulfiram. The cardiovascular effects observed in pretreated animals were similar to those observed in dogs with alpha- and beta-adrenergic blockade or in reserpinized dogs. Inhibition of dopamine-beta-hydroxylase by disulfiram with resultant catecholamine depletion appears responsible for the observed cardiovascular effects.

Intravenous acetaldehyde administration to control dogs resulted in an increase in heart rate and systemic arterial pressure, whereas in disulfiram-treated animals heart rate and arterial pressure fell. The magnitude of the hemodynamic changes observed in both control and treated dogs was essen-

tially proportional to the amount of acetaldehyde infused. Acetaldehyde administration to control dogs increased peripheral vascular resistance but decreased it in pretreated animals. Thus acetaldehyde appears to have markedly different cardiovascular effects in normal and disulfiram-treated animals. Chronic disulfiram administration unmasks the direct vasodilatory and negative inotropic actions of acetaldehyde.

Constant infusion of ethyl alcohol in control dogs resulted in a steady rise in blood alcohol concentrations and significantly increased heart rate, systemic arterial pressure and myocardial contractile force when blood alcohol levels were between 100 and 200 mg/100 ml. However, when alcohol concentrations exceeded 300 mg/100 ml these parameters fell to below baseline values. Constant ethanol infusion to disulfiram-pretreated dogs produced a more rapid rise of blood alcohol concentrations than in control animals, and a marked fall in heart rate, arterial pressure and myocardial contractile force. Increases in blood pressure and heart rate brought about by ethanol at low blood concentrations prob-

ably are secondary to the sympathomimetic properties of acetaldehyde. Furthermore, alcohol itself appears to exert negative inotropic and chronotropic effects on the myocardium.

The findings of Nakano and associates<sup>8</sup> allow an interesting hypothesis. Disulfiram administration produces catecholamine depletion and, in the presence of ethyl alcohol, increased concentrations of ethanol and acetaldehyde. Ethanol and acetaldehyde both have direct depressor effects on the cardiovascular system which, when complicated by epinephrine and norepinephrine depletion, result in peripheral vasodilation and hypotension.

#### MANAGEMENT OF DISULFIRAM-ALCOHOL REACTION

Reliable guidelines to the management of the alcohol-disulfiram reaction are not established. The manufacturer's product information cites an unreferenced, two-page review<sup>18</sup> when advising the clinician on the treatment of typical reactions and states, "When (unusually severe) reactions occur, the usual supportive measures to restore blood pressure and to treat shock should be instituted. Other suggested measures are oxygen by inhalation, carbogen (95% O<sub>2</sub> and 5% CO<sub>2</sub>), intravenous doses of vitamin C (1.0 gm), ephedrine sulfate, or intravenous antihistamines."<sup>24</sup>

Shortly after the introduction of disulfiram, reports of "antidotes" for the treatment of the reaction began to appear.<sup>25-27</sup> Jokivartio<sup>25</sup> and Christensen<sup>26</sup> reported uncontrolled investigations in which iron salts administered intravenously reversed the disulfiram-alcohol reaction. However, no change in acetaldehyde concentrations were observed. It was suggested that "... TETD (disulfiram) easily combines with heavy metals to form insoluble compounds, thus eliminating its (disulfiram's) action on the specific vasodilating receptor cells of the sympathetic system, without affecting the inhibitory action of TETD on the oxidation of acetaldehyde."<sup>26</sup> The validity of this proposal is doubtful. Niblo and associates<sup>27</sup> administered ascorbic acid (0.5 to 2.0 gm) intravenously to 13 patients in an attempt to reverse the disulfiram-alcohol reaction; the rationale for this approach is experimental evidence that disulfiram inhibits cellular oxidative processes and that ascorbic acid appears capable of reversing this inhibition. Each patient served as his own control and experienced two disulfiram-alcohol reactions: one without and one with ascorbic acid. The conclusion was that ascorbic acid "tends to relieve or suppress" headaches, restlessness, palpitations, weakness and apprehension typical of the reaction. However, they observed no effect on acetaldehyde concentration, blood pressure, heart rate or flushing. Their report does not describe the exact experimental design (e.g., did all patients receive ascorbic acid on their first or second reaction?), list specific patient data for both tests, nor subject its results to statistical analysis. It is impossible, therefore, to draw any useful conclusions on the efficacy

of ascorbic acid.

Lester, Conway and Mann conducted an evaluation of iron salts and ascorbic acid, alone and in combination, in a group of 11 patients.<sup>28</sup> Each patient served as his own control and experienced two or three disulfiram-alcohol reactions. Control observations were made during the first test on the fifth day of disulfiram administration; observations of the effects of iron and/or ascorbic acid antidotes were made on either the twelfth or nineteenth day of disulfiram therapy. No alterations in the reaction pattern nor in acetaldehyde concentrations were observed when patients were administered iron salts or ascorbic acid. A weakness of the study was that patients had been receiving disulfiram for a longer period of time when the "antidotes" were evaluated; thus the greater likelihood of more serious reactions on the second or third test might offset a beneficial effect of the antidote.

Nonspecific supportive measures such as Trendelenberg posture, oxygen, and administration of intravenous solute and colloid are probably as effective as any other treatment of the alcohol-disulfiram reaction.<sup>27,28</sup> If such measures do not restore adequate perfusion, use of a sympathomimetic drug is indicated. Ephedrine is often recommended, but it has both direct and indirect-acting sympathomimetic properties<sup>29</sup> and its efficacy may be reduced in the disulfiram-treated individual with norepinephrine depletion. Norepinephrine is probably a better choice of pressor. Intravenous antihistamines are often recommended, but their efficacy is not established. Experimental evidence suggests that histamine plays no role in the hypotensive reaction.<sup>3</sup> Administration of phenothiazine-type antiemetics may be hazardous since their alpha-adrenergic blocking properties may aggravate or precipitate hypotension. Perman<sup>3</sup> could demonstrate no benefit from phenothiazine administration in his experimental studies.

Carbogen<sup>®</sup> is apparently recommended because of the stimulatory properties of carbon dioxide on the sympathetic nervous system. However, the efficacy of this treatment in restoring normal blood pressure during a disulfiram-alcohol reaction never has been evaluated and it is possible that in the disulfiram-treated, catecholamine-depleted patient, the direct vasodilatory properties of carbon dioxide would predominate, and lead to a further fall in arterial pressure.

#### OTHER AGENTS WITH DISULFIRAM-LIKE ACTIVITY

Other drugs possessing disulfiram-like activity include metronidazole, sulfonylurea oral hypoglycemic agents, sulfonamide antibacterials, chloramphenicol, furazolidine, griseofulvin, procarbazine, quinacrine and tolazoline.<sup>30</sup> Patients ingesting alcohol while taking any of these drugs may experience disulfiram-alcohol reactions. Such reactions complicating metronidazole and sulfonylurea oral hypoglycemic therapy are well known. Di-

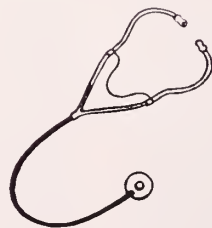
sulfiram can impair the clearance of some drugs (such as phenytoin<sup>31-33</sup> and barbiturates<sup>8</sup>) and potentiate the therapeutic and/or toxic effects of others. Examples include precipitation of central nervous system toxicity due to isoniazid<sup>34</sup> or metronidazole,<sup>35</sup> and potentiation of the hypoprothrombinemic effect of warfarin.<sup>36</sup>

#### ACKNOWLEDGEMENTS

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DAVID E. SMITH  
COMMISSIONER

## Maine Department of Human Services

# “Hepatitis” Outbreak

WILLIAM NERSESIAN, M.D.\*

On Wednesday, May 11, 1977, the Bureau of Health received a call from a school nurse from a Maine junior high school. She stated that three children who attended the school had been diagnosed as having hepatitis. Two were siblings, and their father also had hepatitis concurrently, making a total of four cases. We requested that she gather as much information on these cases as possible and that we would begin an investigation the next day.

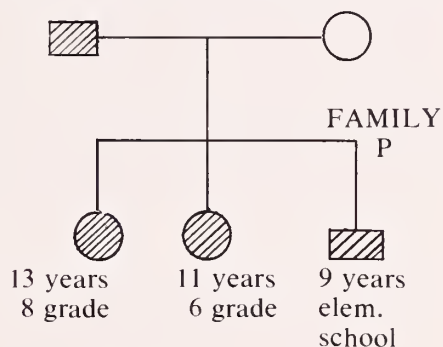
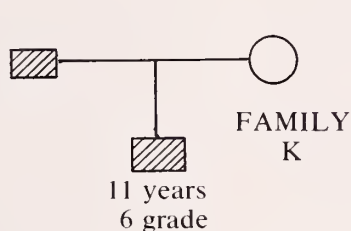
On May 12, a meeting with the school nurse and principal revealed that two more cases had been found, bringing the total to six. The patients were related in the following manner:

were established:

- 1.) five of eight diagnosed patients never had any symptoms.
- 2.) all eight patients (from three different families) had been diagnosed in Dr. A's office, whereas none of the other sources of health care had diagnosed hepatitis since mid-April.
- 3.) the three cases who were symptomatic had experienced only fatigue, with conspicuous absence of anorexia, abdominal symptoms, overt jaundice or other symptoms of hepatitis. The sole exception was the eleven-year-old girl in Family P, who had a long

▨ male case

● female case



The two fathers (both cases) worked together at a local plant. Both eleven year olds set adjacent in the same sixth grade class in the junior high. However, all six cases were diagnosed over a one- to two-week period, and this ruled out person-to-person transmission because the incubation period of hepatitis A (15-45 days, average 30) is too long to permit this. Australia antigens were not done on any of the patients to distinguish hepatitis A from B.

Interviewing was done with Family P in person and Family K via telephone. All the clinics, hospitals and other sources of health care in the local area were telephoned and asked if they had seen any acute hepatitis in their practices within the last month. We learned from Dr. A's receptionist that her two children had been diagnosed as having hepatitis roughly within the same time period. After all interviewing was completed, the following facts

history of multiple complaints long before the present illness. Fatigue in the two fathers was most likely due to the fact that they were working sixteen-hour shifts, six days a week.

- 4.) The highest bilirubin among the six original patients was 2.2. Most of the children's bilirubins were in the range of 1.5 mg% (normal less than one).
- 5.) Only one of eight patients had an elevated SGOT, although some had an elevated urobilinogen by urine dipstick.

These facts pointed to either one of two possibilities: a common source outbreak or a fictitious outbreak due to false-positive diagnoses of hepatitis.

The three families with hepatitis cases had very few things in common to suggest the first possibility. Despite the fact that the two men worked together and two of the children were in the same class, the

\*Maine Bureau of Health, Maine Department of Human Services.

*Continued on Page 259*

**MEETING OF THE ASSEMBLY**  
**American Psychiatric Association**  
**Sheraton Centre — Toronto, Canada**  
**April 29-May 1, 1977**

**Position Paper of the Task Force on Mental Health Centers**

At the May meeting in 1976, the Assembly of the District Branches of the American Psychiatric Association through its Speaker appointed a Task Force on Comprehensive Community Mental Health Centers. Its mandate was to review qualitatively, and by contacting District Branches to report to the Assembly (1) the relation between District Branches and mental health centers and (2) the use made of psychiatrists in patient care within the centers.

Appointed to the Task Force were the following:

John A. Ordway, M.D., Chairman  
Howard Gurevitz, M.D.  
Philip B. Phillips, M.D.  
William B. Spiegel, M.D.  
Frank J. Zorick, M.D.

To carry out its mandate, the Task Force, via telephone conferences during the summer of 1976, constructed a questionnaire to be circulated to each District Branch, and distributed it with a request that the questionnaire be answered early in the fall of 1976 so that the Task Force could organize the material from the responses at the October 1976 meeting of the Task Force, prepare an interim position paper for the 1977 spring meeting of the Assembly, and a more extensive position paper in the fall of 1977.

Analysis of these responses

- A. indicates that many centers which are freestanding and not in conjunction with a viable medical organization are not following the mandate of Public Law 94-63 and the preceding 1963 Mental Health Centers Act, now 14 years old.
- B. highlights the following needs:
  - (1) *Improved patient care in the freestanding center through:*
    - (a) Accessibility of care
    - (b) Prompt triage by a psychiatrist
    - (c) Swift entry into appropriate treatment
    - (d) Treatment by psychiatrists for those in need of specifically psychiatric care
    - (e) Continuity of care
    - (f) Follow-up
    - (g) Increased professionalization of care
    - (h) True 24-hour emergency services
  - (2) *Special Attention to Particular Populations and Programs*
    - (a) The chronic patient and the process of deinstitutionalization
    - (b) Children and adolescents
    - (c) Multiple handicapped persons

- (d) Preventive services to populations at risk
- (e) Services to the socioeconomically disadvantaged and minority groups
- (f) The elderly
- (3) *Improved Interprofessional Relationships*
  - (a) Qualified psychiatrists as directors of clinical services
  - (b) Improved collaboration and sharing of resources between private and public sectors
  - (c) Psychiatric participation in the training of center personnel involved in caring for psychiatric patients
  - (d) Psychiatric supervision of treatment provided by non-psychiatrists
- (4) *Quality Assurance and Evaluation of Care*
  - (a) Quality control systems and accountability for all disciplines
  - (b) Continuing education for all disciplines
- (5) *Adherence to Mandated Functions*

Treatment of the socially maladapted and the mentally ill by close cooperation of the centers' participating disciplines in close adherence to the federal and state laws describing the governance of mental health centers.
- (6) *Well-Organized Administration*
  - (a) *Clinical Administration*
    - (1) Specific treatment policies
    - (2) Precise job qualifications and descriptions
    - (3) Clear enforced lines of accountability
    - (4) Development of an integrated balanced service system to take care of the appropriate medical and nonmedical needs of patients.
  - (b) *Financial*
    - (1) Firm cost accounting
    - (2) Ongoing comparison of cost with private sector
- (7) *Relations of the Centers to the Professional Community*
  - (a) Provision of services not otherwise available in the community
  - (b) Active avoidance of unnecessary duplication of services already provided
  - (c) Appropriate referral to and active informational services about other community resources

**POSITION**

The Task Force on Mental Health Centers takes the position that:

- (1) these issues be forwarded by the Assembly to the Board of the American Psychiatric Association with the request that the Board bring these issues to the attention of the President's Commission on Mental Health
- (2) the life of the Task Force be continued and financed for the entire year so that it can finalize for the Fall meeting of the Assembly its extensive documentation of the issues and its recommendations for action
- (3) At a meeting called by the President of the Association at the earliest convenient time, the Task Force blend its efforts with other components of the American Psychiatric Association which have similar mandates in order to write a combined report. This report would maximize our Association's impact on the President's Commission and other organizations dealing with the mental health centers.

# INCORPORATION OF <sup>35</sup>S L-METHIONINE BY THE RAT WITH STEROID ULCERATION

*Continued from Page 231*

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## BLUE SHIELD "E" AVAILABLE

Blue Cross and Blue Shield of Maine will soon be offering its new, highest paying fixed allowance contract, called Blue Shield "E" Schedule 1850.

Blue Shield payments under this contract will be made according to a fixed Schedule of Allowances. All allowances approximate physicians' mean charges as of June 1, 1977, and are paid on an "up to" basis, not to exceed the professional's charge. The maximum surgical allowance that can be made on a single surgical procedure under the BSE contract is \$1850 (for the most difficult procedure).

In terms of benefit provisions, the BSE 1850 contract is quite similar to the BSC 350 contract (which is now being phased out) and the BSD 450 contract. However, major differences are found in the following areas:

(1) *Diagnostic Laboratory* — BSE will provide Usual, Customary and Reasonable allowances for all laboratory services performed for the diagnosis of a definite illness or injury in the hospital outpatient department, professional's office, or certified independent laboratory.

(2) *Materials and Supplies* — BSE will provide an allowance for specified materials and supplies used in the professional's office. This includes plaster, dressings, wadding, padding, and surgical trays only.

(3) *Surgical Assistant* — BSE will provide 20% of the surgical benefit to surgical assistants assisting on major surgical procedures. Under the BSE contract, major surgical procedures are those scheduled at more than \$140; minor surgery is \$140 or less.

Another difference between the BSD and BSE contracts comes in the area of service benefit levels. The BSE contract includes a service benefit provision with a single income limit of \$6501 and a family limit of \$9501, as compared to the BSD contract's \$5000 (single) and \$7500 (family) service benefit income levels.

Marketing for the BSE contract will begin in July, with benefits to be delivered no earlier than August 1, 1977. Professional Relations representatives will be visiting you to explain some administrative details of the new contract. However, in the meantime, if you have any questions or would like more information, please contact the Professional Relations Department at 1-800-482-0740.

# ABSTRACTS

## Third Biomedical Symposium

### University of Maine at Orono

#### May 26 and 27, 1977

Speakers and titles — no abstracts:

#### *Behavior Session*

**Guest speaker: V. G. Dethier, Zoology Dept., University of Massachusetts.**

"A neural analysis of feeding behavior"

**R. M. Abelson, Dept. Psychology, UMO.**

"Selection for escape from intense noise in *Rattus*."

**R. Collins, The Jackson Laboratory, Bar Harbor.**

"On the inheritance of handedness: a genetics of randomness"

#### *Cancer Session*

**R. E. Eyerer, M.D., Cytopathologist, EMMC, Bangor.**

"Where does cytology (cytopathology) stand today?"

**C. D. McEvoy, Jr., M.D., EMMC, Bangor.**

"Reaction experiences in a tumor clinic"

**John J. McDevitt, IV, M.D., EMMC, Bangor.**

"Endoscopic diagnosis of carcinoma of the G.I. tract"

**John Kaiser, M.D., EMMC, Bangor.**

"Early diagnosis of malignant melanoma"

**Demetrius Traggis, M.D., EMMC, Bangor.**

"Chemotherapy of neuroblastomas"

#### *Cell and Molecular Biology Session*

**Special presentation: C. M. Cohen, The Biological Laboratories, Harvard University, Cambridge, MA.**

"New approaches to the study of mammalian cell plasma membranes"

**A. A. Kandutsch, The Jackson Laboratory, Bar Harbor, Me.**

"The relationship between cholesterol synthesis and cell division"

**A. Messer, Dept. Neuroscience, The Children's Hospital Medical Center, Boston.**

"*In vitro* studies of rat striatal cells"

**D. Morrison, Dept. Biochemistry, UMO.**

"Studies on the limited tryptic cleavage of the gliofibrillary protein"

#### *Human Genetics Session*

**Guest speaker: J. Philip Welch, Halifax, Nova Scotia.**

"Genetic Counseling in Canada"

**L. J. Beauregard, P. H. LaMarche, Genetics Laboratory, EMMC, Bangor.**

"A pericentric inversion of human chromosome C-9: a hypothesis on its meiotic behavior"

#### *Immunology Session*

**Guest speaker: Henry Winn, Transplantation Unit, Harvard Medical School.**

**Catherine Phillips, Dept. Pathology, College of Medicine, Univ. Florida.**

"F<sub>1</sub> hybrid versus parent in the mixed lymphocyte reaction"

**David E. Harrison, The Jackson Laboratory, Bar Harbor, Me.**

"Marrow transplantation across histocompatibility barriers with avoidance of graft versus host reactions"

#### *Virology Session*

**Richard Blake, Dept. Biochemistry, UMO.**

"Fine structure analysis of  $\lambda$ DNA."

**George Todaro, National Cancer Institute.**

Invited lecture on RNA tumor viruses.

#### BEHAVIOR

**Social organization of the grey seal, *Halichoerus grypus***

**D. J. BONESS, Dalhousie University, Halifax, Nova Scotia, Canada**

Eared seal (*Otariidae*) males are territorial during the breeding season, and mating is dependent upon holding a territory. Males of an earless seal (*Phocidae*), vie for status in a dominance hierarchy, and the highest ranking males mate with most of the females. Previous studies of grey seals (another earless species) have indicated that they are territorial during the breeding season, but these studies were only qualitative and did not relate the pattern of behavior to reproductive success. In the present study, spatial patterns and movements of grey seals on Sable Island, Nova Scotia were examined by photographing a fixed area at 40-45-minute intervals each day throughout the breeding season. Detailed records of the behavior of identified animals within this area were made. Females tend to aggregate, especially as they approach estrus. Males are overdispersed, which is territorial-like. Males that succeed in becoming established among females tend to consort with different females over time, though these males also 'defend' other nearby females. Males occasionally move to maintain a position near a particular female, in response to the sexual state of females. Male movement results in overlap in the areas used by different males. Frequent aggressive encounters between males are mainly (96%) non-contact threats and to a lesser extent (4%) fights. These encounters are important in achieving and maintaining a position among females. Males who succeed in becoming established account for nearly all of the observed copulations. Grey seals on Sable Is. are not territorial but consort sequentially throughout their tenure with different females.

**The effects of a juvenile hormone analog on behavioral development in *Drosophila grimshawi***

**J. M. RINGO, Zoology Department, University of Maine, Orono, ME 04473**

The juvenile hormone analog (JHA) ZR515 accelerates the sexual maturation of *Drosophila grimshawi* females. Flies were etherized 24-48 h after eclosion, and 2  $\mu$ l of ZR515 dissolved in acetone at a concentration of 3  $\mu$ l/ml was applied topically to the abdomen; controls received 2  $\mu$ l of acetone. In one experiment, these females were housed with sexually mature males; females were dissected at 9, 11, 13, and 15 d post-eclosion to detect sperm. The JHA accelerated receptivity to males 6 d. In a second experiment, females were maintained as virgins for 16-17 d and then observed in groups of 5 to measure the relative frequencies of 7 behaviors. The JHA groups showed significantly more *abdomen drag* and *slash* than controls. Since previous work had shown that these behaviors increase with age, I conclude that ZR515 switches on these behaviors earlier than normally.

**Pheromonal influences on the agonistic display of *Betta splendens***

**P. M. BRONSTEIN, Psychology Department, Trenton State College, Trenton, NJ 08625**

Research on the chemical influences on the aggressive behavior of Siamese fighting fish will be reviewed. These

animals are capable of detecting the presence of a conspecific, but it now appears unlikely that pheromonal signals can be important in modulating the results of encounters between individual fish.

### **The Role of Sex and Genotype on the Voluntary Alcohol Intake of Mice Selected for Differences in Ethanol-Induced Sleep-Time**

A. C. CHURCH, J. L. FULLER and L. DANN, Department of Psychology, S.U.N.Y., Binghamton, NY 13901

A study aimed at determining whether differences in genetic sensitivity to ethanol-induced sleep-time are correlated with differences in alcohol consumption was undertaken. Mice selected by McClearn and Kakihana (1973) for differences in ethanol-induced sleep-time were used as subjects. In Experiment 1, mice from the long-sleep (LS) and short-sleep (SS) lines were offered a choice of water and solution GS (3% glucose; 0.16% sodium saccharin; w/v), or a choice of water and solution GS+E (GS solution + 4% ethanol w/v). In Experiment 2, mice from the first experiment were provided with a 3-way choice among water, solution GS, and solution GS+E. In both experiments, significantly higher consumption of sweetened ethanol (GS+E) was evident both in SS compared with LS mice and in females compared with males. Both LS and SS mice showed higher intake of GS than of GS+E. In Experiment 1, LS and SS mice did not differ in GS intake, while in Experiment 2, LS mice drank more than SS mice. Thus differences in ethanol intake in both a 2-way choice (water and GS+E) and a 3-way choice (water, GS, and GS+E) are dependent on both genotype and sex. The genetic difference in sleep-time response to ethanol is associated with a genetic difference in voluntary alcohol intake. High sensitivity to the incapacitating effects of ethanol is associated with low ethanol consumption.

### **Taste Responsivity in Genetically Obese Mice (C57BL/6J-ob/ob)**

I. RAMIREZ, The Jackson Laboratory, Bar Harbor, ME 04609

Several researchers have suggested that obese animals increase food or fluid intake more than lean animals when the taste improves and decrease more when the taste gets worse. A series of experiments were conducted to assess this possibility in mice homozygous for the mutation obese. Compared to lean control mice, obese mice did not overrespond to alterations in the sweetness of a milk diet but they did overrespond to the addition of quinine to the milk diet. By avoiding the quinine adulterated milk, the obese mice were depriving themselves of their sole source of food. Therefore the quinine experiment might simply indicate greater tolerance to food deprivation in obese mice. This possibility was tested by maintaining obese and lean mice at 80% of their ad libitum body weights and testing their response to the addition of quinine to the reward in a lick operant device. Obese mice did not overrespond to quinine in this experiment. Response to sweet taste was investigated in preference tests for sweetened and plain water. The preferences of obese mice for sugar and saccharin solutions were similar to or lower than that of lean control mice. Taste preference may be abnormal in obese mice but this abnormality does not fit the picture of overresponse suggested for other forms of obesity.

### **Human Ethology: Behavior Following Thwarted and Non-Thwarted Aggression in Four-year Olds**

D. MÜLLER-SCHWARZE, P. BELANGER, R. G. BUTLER, E. C. WALTZ, and C. MÜLLER-SCHWARZE, Dept. of Zoology, College of Environmental Science and Forestry, S.U.N.Y., Syracuse, NY 13210

The initial goal of the study was to determine motiva-

tional relations behavior and rough-and-tumble play. Four-year old boys and girls were observed in a non-structured nursery school setting. Incidents of aggressive behavior and the preceding behavior between children were observed. The preceding behavior of boys and girls did not differ. We distinguished aggressive behavior that was interrupted by a supervising adult ("thwarted aggression"), and that which went unnoticed by adults ("non-thwarted aggression"). Each "focal child" was observed for 30 min periods, and behavioral changes following the two forms of aggressive episodes were analyzed. Different activity levels and social versus solitary behavior were distinguished. The main result was that thwarted aggression was followed by significant changes toward solitary, and less active behavior. The effect was more pronounced in boys than in girls. No consistent relationships between the two types of aggressive interactions and rough-and-tumble play were detected. The results will be compared with earlier findings on relations between aggressive behavior and play in non-human mammals, such as rats and deer.

### **Maternal Nest-building as Temperature Regulation: The Study of a Complex Adaptation**

C. B. LYNCH, Dept. of Biology, Wesleyan University, Middletown, CT 06457

Nesting serves two functions in small mammals: prevention of heat loss in adults of both sexes, and protection of the young by females. The interrelations between these two types of nesting have been extensively investigated using laboratory mice. Females from lines of mice selectively bred over 10 generations for high and low levels of thermoregulatory nesting demonstrated significant differences in the size of the maternal nest built at 5°C. High-selected females not only built larger nests at all stages of pregnancy and lactation, but they successfully weaned considerably more offspring than low-selected females. By the 14th selected generation, this correlated response of maternal nesting with thermoregulatory nesting was also significant at 22°C. An experiment designed for a more detailed examination of the genetic basis of maternal nesting in a cross between inbred strains (BALB/c1bg abd C57BL/6J) indicated that maternal nesting has a substantially lower heritability than thermoregulatory nesting. These results were substantiated by results of a large parent-offspring regression experiment on females from an outbred stock (HS/1bg). Both studies provided evidence that being raised in a maternal nest may permanently alter adult thermoregulatory behavior. The extent and possible mechanism of this influence will be discussed.

### **Parent-offspring Interactions in Domestic Zebra Finches**

R. E. MULLER, Colby College, Waterville, ME 04901

A study of the parent-offspring interaction during parental feeding in domestic Zebra Finches has shown that the communication system that has evolved is a dynamic one. The signals generated by begging offspring change substantially as they grow and develop. The receptivity of parents to begging signals also changes as the offspring grow. These changes occur in parallel so that the parents are responsive to the correct type of signal at a time when the offspring use it. Visual cues are of primary importance in coordinating parental feeding during approximately the first fifteen days of the nestlings' lives. Subsequently, when the offspring are approximately sixteen to nineteen days old, acoustic cues begin to be used to stimulate parents to feed their offspring. Several of Trivers' (1974, *Am. Zool.*, 14) predictions about parent-offspring conflict were tested and found to be valid for Zebra Finches. Parents stop feeding their fledglings before the fledglings cease begging to their parents. Several measures suggest that this is due to a reduction in the parents' sensitivity to

the begging behavior of their offspring. The offspring displayed several types of behaviors which could be interpreted as competitive. These included an increase in the intensity of begging just subsequent to food ingestion, and the appearance of begging behavior in response to recorded begging calls. Fledglings continue to beg to their parents after they are able to feed themselves. They also retain their mouth markings until well after they become independent. These two traits are probable manifestations of the selective pressure on offspring to increase the period of parental investment.

### Hormones and Aggression

R. GANDELMAN, Department of Psychology, Rutgers University, New Brunswick, NJ 08903

To determine whether prenatal exposure to testicular androgen influences the later exhibition of intraspecific fighting behavior in mice, males and females were gonadectomized within 12 hours of birth. The males fought sooner following testosterone administration during adulthood than did females (15.5 vs 27.6 days, respectively), thus indicating that androgen from the fetal testis influences later responsiveness to testosterone. An additional experiment was performed to determine whether androgen release from the fetal testis affects the display of aggression in females. It was found that females contiguous to male fetuses in utero had larger ano-genital distances and fought sooner in response to adult testosterone exposure than did females contiguous to one or contiguous to no male fetuses. Females contiguous to one male fetus were intermediate on both measures. The results show that prenatal exposure to testicular androgen affects the later aggressive behavior of both male and female mice.

### Neuroendocrine Interactions and Sexual Behavior in the Domestic Chick

C. C. MEYER, Quinnipiac College, Depts. of Psychology and Biology, Hamden, CT 06518

We have been studying the brain controls of developing sexual behavior in the male domestic chick. The behavioral index employed is precocial copulation, a sexual sequence that is stimulus controlled by the prone hand of the experimenter as well as exogenous androgen injections. Our experiments have suggested a number of neuroendocrine correlates for precocial copulatory behavior. Bilateral electrolytic lesions placed in either the medial preoptic or anterior hypothalamic regions disrupt copulatory activity. Progesterone, probably acting as an anti-androgen, has suppressed precocial copulation when placed in the preoptic hypothalamic continuum (POH). Chemical brain implants of testosterone have activated copulatory activity when positioned in the medial preoptic region. We have used the autoradiographic technique to confirm the presence of androgen-sensitive cells within the POH. Moreover, we studied the hormonal sensitivity of these androgen-responsive neurons in the male chick brain as a function of previous endocrine and/or behavioral experience. Results of this study indicated that variable combinations of sexual behavior and exogenous testosterone differentially affect the response of androgen-dependent cells to circulating radioactive testosterone. Implications of these studies for brain behavior interactions and plasticity are discussed.

### Psychobiological aspects of female reproductive system in ring doves (*Streptopelia risoria*)

M. F. CHENG, Institute of Animal Behavior, Rutgers University, Newark, NJ 07102

When a pair of male and female ring doves in a breeding condition is introduced, the male courts and the female

interacts with the male in an elaborate and systematic sequence which culminates in egg-laying. The pair then participate in incubation and rearing the young. This paper concerns the hormonal and non-hormonal factors regulating these behavior changes. The role of ovarian hormones (estrogen, progesterone), pituitary hormones (LH, prolactin) and hypothalamic hormone (luteinizing hormone-releasing hormone) in mediating female behavior changes is examined along two lines: 1) castration — replacement study, 2) radioimmunoassay of the level of hormones throughout the various stages of the normal breeding cycle. While the reproductive behavior changes are clearly hormone-dependent, they are also subject to non-hormonal factors such as breeding experience, male-female familiarity and other environmental cues. Thus, the reproducing system of ring doves is adapted to fine changes of internal and external conditions for maximum success in breeding.

### Sexual dimorphism in *Drosophila grimshawi* and sexual selection in decapod crustaceans

B. GREENSPAN, Department of Biology, Bowdoin College, Brunswick, ME 04011

In the decapod crustaceans, sexual dimorphism is found in many species, and some recent studies suggest that, as in some birds, mammals, and lizards, the differences between males and females are related to their mating systems. R. A. Stein found that in cambarid crayfish, males have larger chelae than females, and male size is related to reproductive success. The enlarged chelae of males do not seem to give males any advantage in predation or in defense, but are used in reproductive activities. In the xanthid crab *Neopanope sayi*, studies of R. C. Swartz show that the largest animals are usually males, the chelipeds are sexually dimorphic, and males are invariably larger than the females which mate with them. In the fiddler crabs (genus *Uca*), the major cheliped is allometrically enlarged in the male, and is used in display. A study of *U. rapax* showed that male size is related to male reproductive success, with females choosing to mate with males who are, in each case, a little larger than the females. Such data suggest that in decapod crustaceans sexual dimorphism is associated with sexual selection, with males competing for females. Other factors may be involved (e.g. effect of female size on ability to produce young, which has been assessed in mammals). Theories of the evolution of sexual dimorphism can be applied to crustaceans as well as vertebrates if common evolutionary mechanisms operate.

### The Genetics of Food Competition

M. E. HAHN, Biology Department, William Paterson College, Wayne, NJ 07470

Food competition between mice presents an interesting and complex social situation. Behavioral variability observed in this situation could be attributed to a number of experimentally controlled variables such as: food deprivation state, genotype, age, sex or general aggressiveness. In addition, since this is a social situation, the status of both competitors must be considered. In order to investigate this situation, a diallel cross of four inbred mouse strains was employed. The diallel cross is a powerful design as it allows partition of behavioral variation into specific genetic and environmental components. Males and females of 16 genetic groups were deprived of food for 24 hours and placed with a competitor of the same sex and either same strain or standard test strain and a .5g piece of food. A number of variables affected the food competition situation. In particular, weight loss during deprivation predicted success in food possession. Individual genetic groups differed in their behavioral tendencies in the situation as animals of some groups fought to dominance be-

fore eating while animals of other groups ate before fighting. Genetic results of this study are interpreted with respect to the evolutionary value of the behavioral traits measured.

#### **Host Recognition and Physical Factor Requirements of the Entomophagous Parasite *Brachymeria intermedia***

D. E. LEONARD, Dept. of Entomology, University of Maine, Orono, ME 04473

*Brachymeria intermedia* (Hymenoptera: Chalcididae) is an internal parasite of lepidopteran pupae. Kairomones, transspecific chemical messengers on host pupae, are critical in host recognition and host acceptance of the parasite. Kairomones are in the paraffin fraction, molecular weight range C-35 to C-40, primarily in the dimethyl substituted compounds, with dimethyl C-33 and dimethyl C-35 showing the maximum biological activity. Host recognition and host acceptance involves a behavioral sequence involving antennal contact with the host, mounting, antennal drumming, grasping of the host, insertion of the ovipositor, withdrawal of the ovipositor, antennal drumming, and departure. Host pupae from which kairomones have been removed by n-hexane are searched by the antennae, but not mounted. On normal hosts, the parasite antennae are maintained at about a 45° angle during the initial search, but when suitable kairomones are encountered, the antennae are brought to the vertical and vibrated up and down rapidly (drumming). Scanning electron micrographs show most contact chemoreceptors in a depression on the antennal tip, and electrophysiological studies are underway to identify kairomone receptors. Most response in bioassays occurs with kairomones washed from gypsy moth pupae, a natural host of *B. intermedia*, with less activity with washes from pupae of greater wax moth or spruce budworm. Oviposition choice experiments show gypsy moth preferred over the other two species. Physical factor requirements show parasite adults are photopositive, prefer warm, dry environments, and have a peak of activity from 1330 to 1530 hours.

#### **The Burial Alarm Response of the Marine Mud Snail, *Nassarius obsoletus***

D. STENZLER and J. ATEMA, Boston University Marine Program, Marine Biological Laboratory, Woods Hole, MA 02543

The marsh mud snail, *Nassarius obsoletus*, shows the strongest self-burial response when stimulated with conspecific extract. Congeneric responses were slightly less pronounced. Taxonomically non-related species caused no response. The response may last as long as 24 hrs due in part to the longevity of the alarm substance in seawater, and in part to mud adsorption. "Memory" may also be involved since alarmed snails stay buried in the absence of the substance. Active release of the substance, which is present in the blood and throughout the snail's tissues, does not occur. Starvation resulted in reduction of alarm responsiveness. Following resumption of feeding, the original responsiveness returned. Of several possible predators, only the green crab, *Carcinus maenas*, elicited the alarm response.

#### **Strength of Aggressive Display in Siamese Fighting Fish (*Betta splendens*) toward a Conspecific, an Alien Species (*Macropodus opercularis*), and a Mirror Image as Affected by Prior Conspecific Visual Experience**

W. M. MILEY and G. BURACK, Stockton State College, Pomona, NJ 08240

Siamese Fighting Fish (*Betta splendens*) were provided with ten days of visual experience with other conspecifics or were visually isolated from them for ten days. *Bettas* were then allowed to display aggressively toward the fol-

lowing stimuli: a conspecific, an alien species (*Macropodus opercularis*), and a mirror image. Differences between intraspecific and interspecific displays depended on the response measure used. Isolated *Bettas* displayed more frequently to conspecifics than to the other two types of stimuli. However, there were no differences in the other response measures (duration of display, latency to first display, and time to absence of responding for 15 minutes) in any of the stimulus conditions. Whether there are differences between intraspecific aggression, inter-specific aggression, and aggression toward a mirror image may depend on the response measures used and the procedures leading up to behavioral testing.

#### **Prey Detection by Lady Beetle Larvae**

R. H. STORCH, Department of Entomology, University of Maine, Orono, ME 04473

Stage IV *Coccinella transversoguttata* larvae detect prey primarily by touch. The larval eyes are not as important as the prolegs and head and mouthparts in detecting prey. When moving larvae contact objects of appropriate size with the prolegs, they pause, turn toward, and touch the object with the head. Larvae passing within 5mm of an object do not pause and turn toward the object. Searching behavior of blinded larvae does not differ significantly from the searching behavior of normal larvae. The searching and cleaning behavior of larvae with impaired prolegs or mesolegs is, however, significantly different from normal larvae. Contact chemoreception by the prolegs probably does not occur. When inanimate objects similar to prey in size, shape, and texture are contacted by the prolegs, the larvae pause, turn toward and touch the object with the mouthparts before rejecting it.

#### **Experiments on Alcoholism ? in Mice**

J. L. FULLER, Department of Psychology, State University of New York, Binghamton, NY 13901

Inherited differences in free choice alcohol intake have been known in mice for many years. The mode of inheritance varies according to the strains that are studied, but rank orderings of strains in terms of preference are constant when different test procedures are used. The amount of ethanol ingested is usually negatively correlated with sensitivity to injected ethanol; thus it seems that in mice intake may be limited by aversive postingestional effects. However, some strains drink substantial amounts of ethanol even when an alternative highly palatable fluid is available. In these strains ethanol appears to have a positive reinforcing effect. Intake could be regulated by the balance between these two opposing types of reinforcement. The level and precision of control as related to genetic strain and concentration of alcohol will be described. The relationship of the proposed control model to addiction will be discussed.

#### **Startle Reaction Times of Flocking and Non-flocking Birds**

P. MOHAN and F. H. HEPPNER, Department of Zoology, University of Rhode Island, Kingston, RI 02881

Birds flying in tight formation (Starlings, sandpipers) differ in the requirement for fast reaction time from birds flying individually, or in loose formation (Robins, sparrows). Using a modification of a laboratory technique for determination of avian startle reaction times (Pomeroy, H. and F. H. Heppner, Anim. Behav., in press) to light flash and auditory startle stimuli, we measured the startle reaction times of tightly flocked species (Starling, *Sternus vulgaris*) and several species of birds which do not typically fly in tight flocks (Dark-eyed Junco, *Junco hyemalis*, White-throated Sparrow, *Zonotrichia albicollis*, and Blue Jay, *Cyanocitta cristata*).

## CANCER

### Early Effects of *E. coli* Endotoxin on a Methylcholanthrene Induced Sarcoma in the Hamster Cheekpouch

D. F. STEVENS and W. STINEBRING, Zoology Dept., University of Vermont, Burlington, VT 05401

The purpose of this study was to determine if tumors grown in hamster cheekpouches could be used to study the hemorrhagic response induced by endotoxin. Male and female golden hamsters, *Mesocricetus auratus*, were transplanted in their cheekpouches with  $10^5$  methylcholanthrene induced sarcoma cells. The cells were maintained in tissue culture. At varying times after transplantation the animals were injected intraperitoneally with a single dose of *E. coli* endotoxin and the tumors observed periodically for damage. Animals treated with endotoxin on days 4 through 8 after tumor transplantation exhibited hemorrhaging adjacent to the tumor nodule, hemorrhaging within the tumor, decreased tumor growth rate, and in about a quarter of cases, necrosis of the tumor. Hemorrhaging adjacent to and within the tumor nodules occurred within 2 hours after endotoxin treatment. Tumors transplanted less than 4 days did not respond to endotoxin. Tumors transplanted 9 days or more did not show hemorrhaging adjacent to the transplant but did show extensive internal bleeding. Normal tissue transplants of kidney, liver and fetal fibroblasts did not exhibit these effects. These results indicate that the hamster cheekpouch can be a useful site for direct and repeated observations of the effects of endotoxin on transplantable tumors.

### Pediatric Radiation Therapy

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Major improvements have occurred in the therapy and prognosis of most childhood malignancies in the last decade. These gains have been made possible by improved diagnostic techniques and more thorough evaluation of disease extent prior to therapy as well as technical improvements in the therapeutic modalities available — surgery, radiation therapy, and chemotherapy. Of greatest importance, these therapeutic techniques have been combined so as to insure a systematic multidisciplinary approach and thereby guarantee the child optimum local and systemic therapy with maximum preservation of function. Using several common pediatric malignancies as examples, principles of this multidisciplinary approach will be demonstrated. Finally, results being achieved currently at the Joint Center for Radiation therapy, Children's Hospital Medical Center, and Sidney Farber Cancer Institute in several of these malignancies will be presented with a brief summation of our therapeutic plans.

### Synthesis and Antineoplastic Evaluation of Mitotane-Analogs

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Adrenocortical carcinomas represent a most serious form of neoplasia affecting humans of all ages. These carcinomas tend to produce a wide variety of biochemical and physiological effects often with local recurrence and a high metastatic disease death rate. In addition, a direct relationship has been established between adrenal cortex cancer to that of cancer of the prostate and breast. To date, the ONLY successful treatment for adrenal cortical carcinoma centers around the use of Mitotane.<sup>®</sup> Patients treated with this drug have displayed evidence of tumor regression and/or remission with significant survival rates. However, extremely toxic side effects severely limit the effectiveness of the drug. Heavy concentrations of a very strong acid, o,p-DDA, have been found and

might well account for the side effects noted by virtually all mitotane patients. The primary objective of the research reported here is to synthesize analogs of mitotane which display its anti-cancer properties but lack the serious undesirable side effects. The analogs are designed in accord with existing knowledge as to the biotransformation and metabolic fate of this drug. Blockade of side-chain metabolism will be achieved by the use of strategically located fluorine- and methyl- groups. Results of our synthetic efforts will be discussed along with rationale for preparation.

### Stimulation of Sterol and DNA Synthesis in Leukemic Blood Cells by Low Concentration of Phytohemagglutinin

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The response of leukemic cells from AKR/J mice to phytohemagglutinin (PHA) was compared to that of normal lymphocytes. PHA stimulated first cholesterol synthesis and then DNA synthesis in both lymphocytes and leukemic cells. The neoplastic cells were, however, much more sensitive to PHA, requiring less time and a lower concentration of the lectin for optimum stimulation as compared to lymphocytes. In fact, the amount of PHA which was required to activate lymphocytes to proliferate, as measured by increases in sterol and DNA synthesis, was inhibitory to leukemic cells. The basal level of cholesterol synthesis and the induction of cholesterol synthesis following PHA activation were depressed in lymphocytes and leukemic cells by treatment with 25-hydroxycholesterol and 7-ketocholesterol. These two oxygenated derivatives of cholesterol are known to be potent and specific inhibitors of sterol synthesis. Blockage of sterol synthesis by these reagents also abolished PHA-activated DNA synthesis in lymphocytes and leukemic cells. These results support a hypothesis that the synthesis of cholesterol is an important event leading to cell proliferation.

### Platinum Anticancer Drugs: Structure, Bonding and Reactivity

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Since the appearance of Platinum drugs in anticancer research, investigations have led in two directions: studies of biochemical mechanisms within the cell and characterization of the drugs themselves. Our efforts have been to pursue the latter of these by correlation of spectral data (absorption, luminescence, NMR, NQR, Raman measurements) with molecular orbital calculations in order to provide chemical bonding criteria for the prediction of anticancer activity. Absorbance and luminescence spectra in solution and KCl pellets reveal a distinct difference between the *cis* and *trans* isomers of Platinum II diamines and dipyridines. Luminescence is thought to come from the lowest d-d transition. However, the intensity varies as a function of temperature with a distinct consistent pattern emerging between the two isomers. Preliminary results reveal the same effect carries over to the yellow Platinum-TMA complexes which are related closely to the biologically active anticancer agents, Platinum Blues. We feel the color of the blue isomorphous form of the Pt-TMA complex arises from a low energy charge transfer band. Our extended Huckel molecular orbital treatments of Platinum II diamine dichloride, both *cis* and *trans*, do indeed show a difference between the ordering of the d orbitals in the two isomers and correlate fairly closely with the energies observed in the spectral data. Analysis such as this may prove to be an invaluable predictive and analytical tool in the future search for more

effective cancer drugs.

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### Suppression of Side Effects and Potentiation of Adriamycin in Tumor Bearing Mice

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Adriamycin, an anthracycline glycoside is actually amongst the most effective chemotherapeutic agents known: the cytotoxic properties of this antitumor antibiotic appears to depend on its ability to interfere with nucleic acid synthesis by complex formation with DNA. Recent interest in the use of adriamycin-DNA complex as an approach to improve the therapeutic effectiveness and to reduce toxicity of adriamycin for cancer chemotherapy requires a better understanding of the properties of such a complex. The latter was prepared by mixing adriamycin and DNA in a drug-polynucleotide ratio 2:1 (w/w) at pH 7.5. Free drug was removed by gel filtration on Bio Gel P-10 and the complex was brought to dryness by pressure ultrafiltration on a PM-10 membrane. A final adriamycin-DNA ratio of 1:10 (w/w) was obtained using this procedure. This complex was then assayed in tissue culture with various normal and tumor cell lines. The cytotoxic efficiency of the complex in vitro varied from one cell line to the other but was found comparable to the free drug. However, when the complex was used in breast carcinoma bearing mice BW 10232 (70 µg Adriamycin/700 µg DNA s.c. every three weeks), we noticed a markedly reduced size of the tumor and an increase in life-span as compared to mice treated with an equivalent amount of the free drug.

This work was supported by the CRSQ and the NCI.

### The origin and development of testicular and ovarian teratomas in mice

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Testicular teratomas originate within the spermatogenic tubules from primordial germ cells during the 13th day of gestation. During early stages of their development they are composed of a layer of embryonal carcinoma cells surrounding a central lumen, and they resemble normal mouse embryos. At a week of age several types of immature tissues are recognizable. At one month of age most of the teratomas are composed of well differentiated apparently normal tissues, but there is no organization. In most cases all of the embryonal carcinoma cells differentiate and the tumors are benign. A few are malignant and can be maintained as transplantable tumors indefinitely. In females teratomas originate from parthenogenetically activated ovarian eggs. Their development is indistinguishable from normal embryonic development for about a week, but then they become disorganized and form teratomas instead of baby mice. Parthenogenesis is very common in inbred strain LT/Sv mice, both in the ovary and in the uterus. Parthenogenetic embryos implant in the uterus and develop apparently normally for about a week, but then they become disorganized and are miscarried. We have fused an 8-celled parthenogenetic egg from a pigmented strain with an 8-cell normal albino embryo and grafted them to the uterus of a pseudo-pregnant female and obtained white mice with black patches. The white was inherited from his normally mated mother and father, and the black from his virgin mother. This demonstrated that even though parthenogenetic mouse embryos cannot survive, their cells are able to participate in normal organ formation.

### The effects of tissue morphology on the regulation of a genetic locus, *Gdc-1*, in tumors

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In the mouse two genetic loci code for the isozymes of 1-glycerol 3-phosphate dehydrogenase ( $\alpha$ -GPDH, EC 1.1.1.8). One locus is expressed in the embryo, fetus, ascites tumors, and in certain cultured cell lines; the other locus, *Gdc-1* on chromosome 15, is expressed in adult tissues and solid tumors. Except for transition periods both loci do not appear to be simultaneously synthesized in the same tissue. Transplantable tumors that reversibly convert from ascites to solid forms also reversibly express the embryonic or adult form of  $\alpha$ -GPDH. This latter finding suggested that the organization of cells in a tissue is important for specific gene expression. This idea is being tested in a reaggregating cell culture system obtained from normal cerebellar cells of neonatal mice. Cerebellar aggregates in culture undergo a process of differentiation both morphologically and with respect to the transition in  $\alpha$ -GPDH isozymic expression that resembles in many ways normal differentiation. C1300 neuroblastoma cells have been co-aggregated with the cerebellar aggregates and the effects on differentiation at the *Gdc-1* locus assessed. The results indicate that undifferentiated cerebellar cells in contact with neuroblastoma cells do not undergo differentiation at the *Gdc-1* locus. This repression of adult enzyme synthesis does not occur if the cerebellar aggregates are fed with conditioned medium from tumor cells nor if the tumor cells are co-cultured in the same flask but in the absence of tight cell-to-cell contact. Cell contact of a neuroblastoma cell and a normal cerebellar cell seems to be required for repression of *Gdc-1* locus in the cerebellar cell.

### Skin tumor induction in immunomodulated mice

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Immunodeficient mice restored with low numbers of normal spleen cells developed carcinogen induced skin tumors earlier than mice that either were not restored or were restored with large numbers of spleen cells. Progression of these tumors to carcinoma occurred most frequently in the mice restored with low numbers of spleen cells. Regressions of the MCA induced skin papillomas occurred more frequently in the mice that received no spleen cells or high numbers of spleen cells.

These results conform with the predictions of the immunostimulation hypothesis by suggesting that the immune response is able to modulate tumor induction and progression.

## CARDIOLOGY

### The Difference Vector: Application to Myocardial Infarction

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The vectorcardiogram (VCG) after an intervention, such as administration of a drug or surgery, is often compared with the control VCG to determine changes. Our approach is to use the *difference* between the postoperative and preoperative VCGs. If a change affects only a portion of the heart, such as a localized infarction, the difference vector should be more indicative of the effects of the change than the postop VCG alone, since the normal components are eliminated. Methods: Infarcts were produced in young pigs by ligating branches of coronary arteries. VCGs were taken both preop and 1-2 weeks postop. The results were expressed in terms of vector spatial magnitude (M) during QRS. The pig has one to three peaks of M, corresponding to excitation of septum,

ventricular free walls, and basal portions of ventricles and septum, respectively. Results: The postop VCGs tended to point away from the infarcted site but the diff. vectors gave a much clearer indication of this. For example, in pig #13 which had a transmural infarct in the LV wall, the preop VCG pointed to left posterior and down. The postop VCG pointed directly posterior and down, but the diff. vector pointed to the right and somewhat anterior and up. In pig #51, the RV was also ischemic. The M<sub>1</sub> control vector pointed to right anterior and horizontal. After ligation, the diff. vector pointed to the left anterior and upwards, away from the RV. We conclude that the diff. vector is more specific in indicating infarction than the postoperative vector alone.

#### **A New Technique for Carotid Sinus Isolation in the Dog**

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Pressure sensitive cells in the wall of the carotid sinus provide input for rapid adjustment of systemic arterial pressure. In order to study this negative feedback control of blood pressure over a wide range of input pressures, the carotid sinus must be isolated from the rest of the systemic circulation. Classically a "blind sac" preparation is made by the Moisejeff technique in which all vascular branches from the sinus are surgically ligated. The surgical approach is lengthy and often results in damage to the baroreceptor area, or even to complete denervation. We have developed a technique for carotid sinus isolation which involves minimum surgery and is quick, simple and reliable. In 20 mongrel dogs (15-20 Kg) anesthetized with  $\alpha$ -chlorolose, the common carotid arteries were cannulated with flow-through cannulas 1 cm below the sinus. The internal carotids were ligated 2 mm above the sinus and the external carotid arteries were cannulated with PE90 tubing in a down stream position. A solution of Avitene (microcrystalline collagen hemostat), 100 mgs/1 ml saline was made and a 1 ml amount injected into both external carotid cannulas. The Avitene solution was distributed into the patent vessels of the sinus region and quickly blocked them. Excess Avitene was washed out through the common carotid catheter. An intrasinal pressure as high as 300 mmHg could be maintained with this preparation for several hours. The gain of the response curve of systemic arterial pressure to changes in intrasinal pressure was high, indicating maximal responsiveness of the system.

### **CELL AND MOLECULAR BIOLOGY**

#### **Isolation of a Reconstituted Lipid-Protein Complex from Human Erythrocytes — An Influenza Virus Receptor**

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A model system was developed to study the attachment of a virus to a cell surface membrane. The system under study utilizes influenza virus (H<sub>2</sub>N<sub>2</sub> strain, A<sub>2</sub>/Japan-305/57) and hemoglobin-free human erythrocyte membranes. Solubilization of human erythrocyte membranes was achieved using the nonionic detergent octyl glucoside (Baron, C. and Thompson, T. E., Biochem. Biophys. Acta, 382: 276, 1975). A solubilized supernatant fraction (100,000 x g for 1 hr) consisting of proteins, lipids and N-acetylneraminic acid containing components, were fractionated on a column of diethylamino-cellulose in the presence of 30 mM octyl glucoside with gradients of NaCl. Reconstituted membrane particles were produced from the eluate at 2 M NaCl by dialysis and isolated by isopycnic centrifugation. The reconstituted membrane particles yielded two sharp bands of only slightly different density from each other. These particles (both densities) could attach (I<sup>125</sup>)-labelled virus and inhibit hemagglutination of

hen erythrocytes. Analysis of the less dense reconstituted membrane particles demonstrated the presence of a sialyl-glycoprotein with an apparent MW of 41,000 (PAS 2), a protein with a MW of 28,000, sialyl containing glycolipids and, almost exclusively, the phospholipids sphingomyelin and phosphatidylcholine.

#### **Identification of a Nucleoside Tri- and Diphosphohydrolase in the Pig Pancreas**

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A nucleoside tri- and diphosphohydrolase activity has been found in the pig pancreas. The enzyme catalyzes the hydrolysis of ATP or ADP to the nucleoside monophosphate AMP. With both of these substrates, the activity is maximum at pH 8.5. The enzyme requires Ca<sup>2+</sup> or Mg<sup>2+</sup> ions (optimal concentration, 5 mM). The enzyme is associated with the particulate fraction of the homogenate and is preferentially located in a microsomal fraction. The enzyme shows good stability and can be kept for weeks at low temperatures without any significant loss of activity. Substrate specificity has been assessed with a variety of nucleotides and other phosphorylated substrates. Denaturation curves by heat or proteolytic digestion seem to indicate that there is only one enzyme involved in the hydrolysis of both substrates (ATP or ADP). The enzyme has also been detected in the rat pancreas. Work is in progress to further purify this enzyme which might play a key role in the control of calcium concentration in the different cell compartments.

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#### **The Intermediate (80-100 Å) Filament**

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Cytoplasmic filaments, 80-100 Å in diameter are present in many tissues and particularly abundant in brain. These filaments are intermediate in diameter between microtubules and actin microfilaments, the other two major constituents of the cytoskeleton. The evidence presently available suggests a close relationship between the protein subunits of intermediate filaments in different types of cells, so that intermediate filaments, as microtubules and microfilaments, may form a distinct category of cytoplasmic organelles not only on a morphological basis but also on chemical grounds. The finding indicating that intermediate filament proteins are covalently associated into large species by intermolecular disulfide bridges may explain their remarkable stability compared with microtubules and microfilaments. Plastic changes during development and neuronal remodeling may be achieved by limited proteolysis resulting in the breakage of intersubunit linkages. Although sharing common properties the protein subunits of intermediate filaments in different tissues still retain a remarkable degree of cell specificity as indicated by immunochemical studies.

#### **Cytochrome c Oxidase Activity in T/t<sup>6</sup> (Balanced Lethal) Mutant Mice**

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Cytochrome c oxidase (ferrocytochrome c: oxygen oxidoreductase, E. C. 1.9.3.1), an enzyme complex of the mitochondrial inner membrane consisting of several polypeptides, functions as the terminal oxidase of the respiratory chain. Genetic regulation of its activity occurs by both the nuclear and mitochondrial genomes. Mutations in both genomes are known to occur in yeast and Neurospora that cause a reduction of cytochrome c oxidase activity. Assay of respiratory chain enzyme activ-

ities in liver mitochondria preparations of *T/t<sup>6</sup>* (balanced lethal) mutant mice demonstrate a reduction of cytochrome c oxidase. Only cytochrome c oxidase activity, calculated as units per  $10^{10}$  mitochondria, was significantly lower in both R-1 and R-2 fractions of *T/t<sup>6</sup>* mice. Developmental studies indicate that cytochrome c oxidase activity may be abnormal early in postnatal life. The *T/t<sup>6</sup>*-locus, a complex genetic locus on chromosome 17, may contain cistrons important to the function and biogenesis of mitochondria.

#### Diffusional Effects on Nuclear Spin-Lattice Relaxation in Biological Cells

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Protons in water can be polarized and the resulting magnetization decay monitored by pulsed NMR techniques. For bulk water the decay is a simple exponential; for small samples (e.g. biological cells) the decay is more rapid and non-exponential. A theory for this effect is presented based on diffusion of water in the volume and spin relaxation at the surface of the cell. The classical diffusion equation is solved for several model geometries. The result is a non-exponential decay quantitatively similar to that observed in experiments.

#### Dispersal of Mammalian Cell Aggregates Using a Vortex Whistle

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The inability to disperse aggregates of biological cells without morphological damage or decrease in viability is a serious problem in biological research and medical diagnostic procedures. The vortex whistle as described here offers a possible solution to these problems. In this system, biological cells are forced by a hydraulically driven syringe to flow through a 14 gauge needle, tangentially enter a swirl chamber (1 cm i.d.), pass through a region of smaller diameter and finally exit through a small orifice. It has been found that the dispersal efficiency of the vortex whistle is increased by the use of inserts within the swirl chamber as well as threading its inner surface. The dispersal efficiency of the system has been tested using aggregates of cultured monkey kidney cells. For these cells the threshold discharge rate for dispersal is  $4 \text{ cm}^3/\text{s}$  corresponding to a shearing stress of  $350 \text{ d}/\text{cm}^2$ . The percent dispersal increases to 85% for discharge rates of  $13.6 \text{ cm}^3/\text{sec}$  corresponding to a shearing stress of  $2,100 \text{ d}/\text{cm}^2$ . Light microscopy indicates that the cells are morphologically normal. Electron microscopy of the cells will also be discussed. This work was supported in part by The National Institutes of Health via grant GM 20514-04.

#### Chemical synthesis of c-DNA for Isolation of fibroin mRNA

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Fibroin mRNA (16,000 base pairs) from the silkworm *Bombyx mori* is composed predominantly of two reiterated and alternating triplets, GGU(gly) and GCU(ala). The chemical synthesis of the complementary DNA 5'ACCAGC 3' (c-DNA) was achieved using a new phosphotriester approach described recently for synthesis of di- and trinucleotides. (Cashion et al., Tetrahedron Letters, 42 (1976) 3769) Partial and complete digestion of the hexanucleotide with venom phosphodiesterase is consistent with the assigned structure. The self-condensation of the hexanucleotide to  $-(\text{ACCAGC})_n$ ,  $n=2,3,4$  and subsequent attachment to cellulose to form an affinity column for more efficient isolation of fibroin mRNA is discussed. The annealing specificity of the synthetic c-DNA to fibroin mRNA is indicated by the fact that the resulting

hybrid duplex is susceptible to hydrolysis by calf thymus RNase H under conditions wherein the corresponding mixture of cDNA and rDNA remains intact.

#### Observations on the Effects of Controlled Dietary Conditions on the Intestinal Histology of *Fundulus heteroclitus*

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The anatomy and the histology of the digestive tube of the cyprinodontiform fish *Fundulus heteroclitus* has been described, together with the effects of starvation on the histological composition of the digestive tube (Ciullo, R. H., 1975. The Pathology of Fishes, University of Wisconsin Press). The effects of controlled dietary conditions on the histological composition of the digestive tube are described in the present investigation. In the carbohydrate and protein fed series of fish, the major evidence of digestive/absorptive activity appears in the distal portion of the posterior intestine and the anterior rectum. The gradual change in the size of food vacuoles in these regions and the absence of granular contents in many of them from 3 to 9 hours after a meal of white bread, suggests a rather constant rate of digestion and absorption of carbohydrate foodstuffs. The variability in the size and in the presence of food vacuoles in different fish from 3 to 9 hours after a meal of crab meat, suggests a less constant rate of digestion and absorption of protein foodstuffs. The evidence from the series of fish fed a meal of dogfish liver, as correlated with the absorption of neutral lipids, tends to reinforce the conclusion that the major digestive/absorptive activity in *F. heteroclitus* occurs in the posterior intestine and the rectum.

#### Steroid Hormones, Gonad Development and Sexual Differentiation in the Nematode, *C. elegans*

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*C. elegans*, a soil nematode, normally develops as a hermaphrodite. Occasionally a male arises from the population. The hermaphrodite has the genotype of X/X and produces both sperm and eggs, resulting in self-fertilized progeny. The males arise from the non-disjunction of the X/X chromosomes to give an X/O genotype. These animals only produce sperm and possess a copulatory organ, the bursa, for mating. In other organisms it had been shown that the sex steroids, estrogens and androgens, influence sexual differentiation. We have been able to isolate some mutants of *C. elegans* in which these aspects of sexual differentiation are altered. In addition, some biochemical studies of steroid interactions have been undertaken. We shall describe the genetic, morphological and biochemical characterizations of the wild type *C. elegans* and some of its mutants. The potential for isolating a large number of sexual differentiation mutants and their biochemical and genetic analyses may provide a unique system for revealing the genetics of steroid influences on sexual differentiation.

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#### Functional Relationship of Cholesterol and Cytoskeleton Components in Mammalian Plasma Membranes

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The sterol in mammalian plasma membranes can be depleted up to 50% by blocking the de-novo synthesis of cholesterol with oxygenated derivatives of cholesterol

which specifically depress the activity of the rate limiting enzyme, HMG-CoA reductase, in the cholesterol synthetic pathway. Such depletion of membrane sterols in mouse L-cells reduces or abolishes endocytosis, i.e. the uptake of solutes by formation of membrane vesicles.<sup>1</sup> In L-cells with a normal sterol content endocytosis is temperature dependent and no breaks in Arrhenius plots are detectable, i.e. no thermotropic phase transitions are evident. In L-cells with reduced sterol content a break in the Arrhenius plot is observed within a temperature range of 16°C to 19°C. Below this temperature range the rate of endocytosis is similar between the control and sterol deficient cells but above this temperature the rate in sterol-deficient cells is greatly reduced. Cells treated with drugs which affect the cytoskeleton (microfilaments and microtubules) also severely reduce endocytosis. However unlike cells treated with the sterol inhibitor no breaks in the Arrhenius plot are observed. These results lead us to hypothesize that cholesterol through its modulation of the fluidity of the plasma membrane may create an "anchor-environment" required for the cytoskeleton to execute membrane deformation. Experiments to substantiate this hypothesis will be discussed.

<sup>1</sup>Heiniger, H. J., et al. *Nature* 263, 515, 1976.

### The Inactivation of Malate Dehydrogenase by Ultrasonically Produced Shearing Stress

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Malate dehydrogenase has been exposed to ultrasonically produced shearing stresses for periods up to 90 minutes. The enzyme was sonated by placing a resonant length of 0.025 cm diameter tungsten wire into the 0.3 ml sample and driving the wire in transverse oscillation at 20 kHz. After sonation, the enzyme activity was assayed spectrophotometrically. The enzyme was found to be inactivated for wire displacements greater than 30 microns. Since no temperature rise or cavitation were detected in the treatment vessel, the mechanism of inactivation is believed to be shearing stresses associated with the acoustic microstreaming occurring near the wire tip. For conditions of the experiment, the magnitude and duration of the shearing stress are respectively 3000 d/cm<sup>2</sup> and 2 m sec. The enzyme was inactivated at an exponential rate which was dependent on enzyme concentration. For conditions such that the minimum activity was 10 units per milligram, the inactivation constant was 0.023 min<sup>-1</sup> while for a concentration 10 times greater the inactivation rate was less with a constant of  $1.4 \times 10^{-3}$  min<sup>-1</sup>. This work was supported in part by a grant from the Maine Heart Association.

### Secretion in the C57B1/6J Anterior Pituitary — Proposed Mode for Animals Under Stress

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It is generally accepted that exocytosis is the main mechanism of hormone discharge in the anterior pituitary. This study was designed to investigate the possibility of an alternative mode of secretion active during times of hormonal stress. C57B1/6J female mice were killed by cervical dislocation and pituitaries removed on 0, 4, 12, & 18 days of pregnancy and 6 days post-partum. Ultrastructural examination of the anterior pituitaries on days 12, 18 pregnancy and 6 days post-partum revealed multiple granule release from somatotrophs and mammotrophs via rough endoplasmic reticulum and Golgi fusions with the plasma membrane. Whereas exocytosis is responsible for normal levels of hormone release, multiple granule release may provide the means for rapid "surges" in pituitary hormone content.

### The Pathway of Glutamate Oxidation in Mitochondria isolated from the cellular slime mold, *Dictyostelium discoideum*

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The pathway of glutamate oxidation is of considerable interest to an organization like *Dictyostelium discoideum* which depends upon endogenous protein catabolism for energy during differentiation. Earlier workers (Wright et al., *Biochem. Biophys. Acta*, 71, 45, 1963) demonstrated that  $\alpha$ -ketoglutarate is a direct intermediate in glutamate oxidation. This  $\alpha$ -ketoglutarate could arise either by oxidative deamination of glutamate by glutamate dehydrogenase or by transamination of glutamate with either pyruvate or oxaloacetate. We postulate that the observed 7-fold increase in the rate of glutamate oxidation during differentiation may be partially attributable to a transamination pathway. To date, we have localized glutamate dehydrogenase, alanine aminotransferase and aspartate aminotransferase activity in the mitochondria of *Dictyostelium amoebae*. Incubations of intact mitochondria with mixtures of substrates (glutamate, pyruvate, oxaloacetate) have confirmed the conversion of glutamate to aspartate. Experiments are in progress to determine the importance of the two pathways in the increase of glutamate oxidation during development.

### Spectroscopic Studies of Zinc(II) and Calcium(II) Binding to Muscular Parvalbumins

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A parvalbumin-like protein (MW = 12,000, pI = 3.0) has been isolated from the skeletal muscle of the arthropod, *Limulus polyphemus*. While low levels of calcium were found bound to the protein, significant levels of zinc were detected, consistent with the high histidine content. Zinc(II) binding was examined in equilibrium dialysis experiments by monitoring  $\gamma$ -emission (1.1 MeV) from <sup>65</sup>Zn(II), employing a Germanium(Li) semiconductor detector. Failure of the protein to release bound zinc upon addition of zinc chelators in the presence and absence of the protein denaturant, guanidine hydrochloride, is suggestive of very tight binding. Consistent with the apparent rigidity of the protein is the finding that the aromatic absorbance of the protein is insensitive to concentrations of 2-propanol up to 5 molar; however, following incubation of the protein with dithiothreitol, the protein absorbance becomes solvent dependent. This is strongly suggestive of the presence of disulfide bonds. In separate experiments on a vertebrate parvalbumin from carp (*Cyprinus carpio*), calcium(II)-induced conformational events were followed by fluorine-19 NMR, employing the sulfhydryl-directed NMR probe 3-bromo-1,1,1-trifluoropropanone.

### Carbon-13 Magnetic Resonance Approach to the Study of Conformational and Dynamic Events in Calcium Binding Proteins

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Natural abundance carbon-13 NMR can be employed to investigate conformational and dynamic aspects of metal ion and substrate binding to proteins as well as protein-protein interactions. Interpretation of chemical shift data, in terms of local conformational events, is most accurate when based on the observation of single carbon resonance

signals. The use of difference spectroscopy for spectral regions exhibiting large chemical shift non equivalence can also be informative. Information on the overall rotational motion of a protein and local segmental motions of particular side chain groups can be obtained by interpretation of measured spin-lattice relaxation time and the muscle calcium binding parvalbumins from *Cyprinus carpio* (Opella, Nelson, and Jardetzky, J. Chem. Phys., 64, 2533-35, 1976 and Nelson, Opella and Jardetzky, Biochemistry, 15, 5552-60, 1976) and phospholipase A2 ( $\alpha$ -form) from *Crotalus adamanteus*.

#### Synthesis of Cytochrome c Oxidase by Isolated Mitochondria

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Cytochrome c oxidase (C.O.) was purified from rat liver mitochondria (Mt) by affinity chromatography on cytochrome c-Sepharose and poly-L-lysine-Sepharose. The active enzyme (10.5-13.4 nmoles heme a+a<sub>3</sub> per mg protein) migrates as a single band during polyacrylamide gel electrophoresis (PAGE) under non-dissociating conditions. SDS-PAGE resolves the enzyme into 6 peptides with apparent MWs of 66K, 39K, 23K, 14K, 12.5K and 10K daltons. Antiserum against this preparation added to crude C.O. inhibits C.O. activity, precipitates all heme a and forms a single Ouchterlony precipitin line. Immunoprecipitation studies using *in vivo* <sup>3</sup>H-leucine-labeling reveal all 6 C.O. peptides can be detected by their leucine content. The ability of isolated Mt to synthesize C.O. peptides was studied using <sup>3</sup>H-leucine in the presence of cycloheximide which inhibits any contaminating cytoribosomes. Analysis of immunoprecipitates from these labeled Mt show that the 66K, 39K, and 23K dalton peptides contain <sup>3</sup>H-leucine. This suggests that isolated Mt can synthesize completed peptide components of C.O. This is consistent with the results of *in vivo* studies in other labs which show that C.O. components >19K are synthesized on mitoribosomes while those <19K are synthesized on cytoribosomes.

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#### Studies on Bacterial Luciferase: The Reaction of the Luciferase-FMNH<sub>2</sub> Complex with Oxygen

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Bacterial luciferase and oxygen associate to form a tight 1:1 complex. In bioluminescence, this complex reacts with oxygen, yielding a relatively long-lived reduced flavin-oxygen adduct, which reacts in turn with a long-chain aliphatic aldehyde to produce light. In the experiments described here, the reaction of the luciferase-FMNH<sub>2</sub> complex with oxygen at 2° has been studied by monitoring absorbance changes (over the range 350-600 nm) with time using the stopped flow apparatus. At 380 nm (isosbestic between the reduced flavin-oxygen adduct and FMN), a rapid absorbance increase occurs first, followed by a slow absorbance decrease, followed by an even slower absorbance increase. At 600 nm, where charge-transfer and/or radical species should absorb, similar changes were observed, but the absorbance excursions were small relative to those at 380 nm. The velocity of the first event appeared to be directly proportional to oxygen tension ( $k$  about  $8.7 \times 10^5 M^{-1}s^{-1}$ ), while the velocities of the second and third events ( $4.5 s^{-1}$  and  $0.54 s^{-1}$ , respectively) were oxygen-independent over a 10-fold range of oxygen tension. These results suggest that a reduced flavin-oxygen adduct is formed in a rapid bimolecular process and then undergoes relaxation or rearrangement into a form (postulated to be a flavin hydroperoxide)

which is relatively stable. The nature of the rapidly-formed adduct is at present unknown. Supported by NSF grant (BMS 74-23651).

#### Protein Hormones and the Eukaryotic Genome

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Historically, hormones and vitamins were thought to act similarly, the main difference being that the latter had to be supplied in the diet. Now, however, we know that they are fundamentally different, for vitamins participate in metabolism as co-enzymes, whereas hormones do not; instead, they trigger or direct metabolic events. There is good evidence that this primary triggering event occurs at the genetic level, and that in the case of steroids, at least, hormones act as positive genomic regulators, i.e., as activators rather than inducers. Protein and peptide hormones as well as others which do not enter the cell, but are recognized by specific membrane receptors, present a more formidable problem. If these hormones also act at the level of the genome — as they must, if they are to continue to deserve the name "hormone" — then the big question is how the specific hormone-receptor interaction can be translated into a hormone-specific signal recognized by the genome. That cAMP alone cannot fulfill this function has been recognized by Sutherland himself. Not only does this nucleotide lack specificity, i.e., all cAMP molecules are alike regardless of which hormone triggered their synthesis, but there also is no specific or consistent correlation between cAMP levels and hormone activity. Nevertheless, it is interesting to note that cAMP is a common activator in procaryotes; and if combined with a suitable, hormone-specific aporegulator operationally equivalent to the intra-cellular steroid receptors, it could act as a specific genomic activator. A hypothesis on how this could be accomplished will be presented, taking into account the structures and properties of the membrane receptors on the one hand, and those of the eukaryotic genome on the other.

#### Template activity of normal and SV40-transformed WI-38 human diploid fibroblasts

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Nuclei isolated from log-phase normal WI-38 and SV-40 transformed WI-38 cells were used as templates for RNA synthesis *in vitro* using homologous or *E. Coli*. RNA polymerases. Transformed nuclei showed a greater capacity for RNA synthesis. Extraction of chromatin from transformed cells with 0.35M NaCl yielded loosely bound nonhistone chromosomal proteins (INHCP) in association with low molecular weight RNA (SnRNA). This fraction showed two different activities: a stabilization of homologous RNA polymerase and an increase in the template activity of normal nuclei to a level indistinguishable from that of transformed nuclei. The same fraction obtained from normal WI-38 cell chromatin had no effect when tested on both types of nuclei. Isolation and purification of the protein and RNA components from the extract showed the INHCP component to be responsible for the homologous RNA polymerase stabilization. However, the SV-WI-38 SnRNA alone increased the transcriptional activity of WI-38 nuclei to a level indistinguishable from that of SV-WI-38 nuclei. Further characterization of the SnRNA will be discussed along with postulated role in gene regulation in general and viral transformation in particular.

#### Control of Cell Division in Ocular Tissue

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Cell division in the lens epithelium of the frog is dependent on pituitary factors. Hence 3-4 weeks after hypophysectomy no cells are found in either S or M. A few cells stall in G<sub>2</sub>. One week after initiation of replacement therapy with bovine growth hormone cells are observed in all four cycle stations. This effect is also achieved by injection of GH and prolactin isolated from frog pituitary glands but not by mammalian prolactins. Serum from hypoxed animals fails to sustain a mitotic activation *in vitro*. The block is overridden by addition of serum from either intact or GH injected hypoxed organisms. At least 2 days of administration are required to produce a mitogenic serum. When lenses from intact and hypoxed animals were explanted to medium containing active serum cells on the former reached S 12 hours later than those in the latter. When lenses were pre-incubated for 2 days in medium containing serum of hypoxed animals and then explanted to active medium those from intact animals again reached S much earlier. (3 days as opposed to ½ day.) Proliferation in frog corneal epi- and endothelium is insensitive to pituitary manipulation.

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### Subunit structure of prokaryotic nucleohistone

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A freeliving thermophilic mycoplasma, *Thermoplasma acidophilum*, is unusual among prokaryotic organisms in that a histone-like protein is tightly bound to its DNA. Histones are otherwise assumed to be associated with only the nuclear DNA of eukaryotes. Since eukaryotic histones can function to condense DNA into compact subunits, and this may be important in storing the greater amount of genetic information in higher organisms, it is of interest to also examine the subunit structure of *T. acidophilum* nucleohistone. Thus the isolated nucleoprotein was digested with a nuclease that selectively removes the DNA not protected by histones. Following digestion, fragments of DNA were recovered that were 48 base pairs long, with many of these molecules containing single-stranded nicks at 24 base pairs. When the nucleohistone was reacted with dimethylsuberimide, which covalently crosslinks the histone molecules that are associated in the same subunit, the histones were found to exist mainly as dimers. In addition, in pure solutions of the histone, tetramers, hexamers, and octamers were also detected. Thus the nucleoprotein appears to be organized into subunits of histone dimers, each associated with 48 base pairs of DNA. This is in contrast to eukaryotic chromatin, which exists in subunits of 8 histone molecules that protect 140 base pairs of DNA. Thus, *T. acidophilum* may represent a primitive level of nucleoprotein organization, consistent with the possibility that it is evolutionarily intermediate between prokaryotic and eukaryotic cells.

### Solution Structures of tRNA's by High Resolution NMR

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A comparison of the crystal and the solution structure of yeast tRNA<sup>Phe</sup> has been carried out by calculating the low field NMR spectrum from refined X-ray structure coordinates. The similarity between the computed and observed spectra show that the crystal and solution structure are virtually identical.

### Induced increases of enzyme activity in the chick pineal gland in organ culture

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The characteristic pineal neurohormone melatonin is formed from *L. tryptophan* through the activities of serotonin-N-acetyltransferase (SAT) and hydroxyindole-O-methyltransferase (HIOMT) enzymes. Levels of activities of these two enzymes in the pineal vary in different ways in response to environmental lighting conditions. We are attempting to identify the factors regulating these responses by studies of the gland in organ culture. Substantial increases in levels of SAT activity are induced by dibutyryl cyclic AMP, inhibitors of cAMP phosphodiesterase activity and halucinogenic amine metabolites of tryptophan. Increased levels of HIOMT activity are induced by hydrocortisone and somatotropin.

### DNA Damage and Repair in Primary Cultures of Rat Hepatocytes

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DNA damage and repair in primary cultures of liver parenchymal cells (hepatocytes) treated with various chemical agents was studied employing alkaline sucrose gradient centrifugation and determination of repair synthesis using unscheduled DNA synthesis and equilibrium density centrifugation. Hepatocytes were isolated employing the collagenase perfusion technique. The cells were inoculated into collagen coated culture dishes using supplemented, serum-free Waymouth's medium. The medium was changed after 6-8 hours and again 12 hours later. The cells were then treated with the various chemical agents. Unscheduled DNA synthesis (repair) increased in a dose dependent manner following treatment of the cells with 2-acetylaminofluorene (AAF) indicating the ability of the cells to activate this phohepatocarcinogen. Comparable amounts of repair were detected following treatment with equimolar amounts of AAF and 3-methyl-4-dimethylaminoazobenzene, both potent hepatocarcinogens; less repair was observed after treatment with 4-dimethylaminoazobenzene and 2-methyl-4-dimethylaminoazobenzene. That the response represents actual repair synthesis was confirmed using equilibrium centrifugation. Alkaline sucrose gradient centrifugation was used to detect DNA damage in hepatocytes treated with several amino acid derivatives constructed to cause base alkylation. *In vivo* studies indicated that one of these compounds enters the liver cells and damages DNA whereas another does not. Similar results were observed with the cultured hepatocytes. Overall, these results indicate that the cultured hepatocytes represent a potentially powerful cell system to screen chemicals for their ability to damage DNA.

## HUMAN GENETICS

### A History of Human Genetics in Maine

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In the United States, education, research and services in human genetics have developed for the most part within university departments of genetics and in medical school complexes. This was not so in Maine. Although Maine lacks these two resources, the state has benefited from various early and innovative activities in the field of human genetics. These activities originated quite independently and occurred in different settings. This paper will record these activities and some of the details of the people, institutions, and stimuli which have led to development of human genetics in Maine.

## **Chromosomal Banding and Gene Location in Humans**

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Chromosomal banding has opened the way to assignment of genes to specific regions of mammalian chromosomes. Although there are some limitations on the precision of gene assignment, the combination of cytological and genetic mapping can now be used to define very closely clusters of genes with respect to chromosomal segments. Since banding patterns do not vary substantially in cells of different tissues or at different stages and since different staining procedures enhance (rather than alter) specific regions of the basic pattern, these banding patterns probably reflect the underlying genetic organization of the chromosomes. Several genes in humans and mice have been assigned to specific chromosomal segments. In both mouse and human preliminary gene assignments, as well as related studies, indicate that Mendelian genes may be localized in specific regions of the chromosomes. Although at least three homologous gene clusters between human and mouse have been identified, the banding patterns have not been conserved. These kinds of evidence suggest that the banding patterns reflect the nature of chromatin in specific chromosomal regions. The assignment of increasing numbers of genes to specific chromosomal regions will not only lead to a better understanding of the structure and function of mammalian chromosomes but will also have direct benefits to medicine: (1) in helping to understand the mechanisms in many genetic diseases and (2) in aiding diagnosis of hard to identify diseases through linked markers.

## **The Genetics of Hypospadias**

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Hypospadias (H) occurs as a minor feature of several genetically transmitted syndromes. Isolated H — i.e., H without significant associated abnormalities other than penile or minor genital anomalies — is known to show occasional familial aggregation. A recent large population study (Mayo Clin Proc 49:52 1974) concluded that the etiology of H was multifactorial and perhaps polygenic. Fathers were affected in 4 of 107 families, and in 2 of these 4 families there were two affected sibs. There were 5 additional affected sibling pairs. An earlier Danish study found 7% rate of affectedness among first-degree relatives and a 50% concordance in twins. The present report presents five instances of familial aggregation of mild glandular H observed in a pediatric practice: a pair of affected twins with a normal father; a pair of affected siblings with normal father; a pair of affected siblings with affected father; an affected child, father and probably-affected grandfather; and an affected child, father, and paternal grandfather. The 4 fathers known to be affected had 5 sons — all affected. An additional father thought to be affected had 4 sons of whom at least one was affected. Experience with these families indicates that estimates of involvement of relatives of persons with H are probably grossly low, especially for mild H. Thus the higher rate of first-degree relative involvement in severe cases, used to support polygenic inheritance, may be artifactual. The observations here reported raise the question of possible Mendelian inheritance of isolated H in some families.

## **Inbreeding in human communities in Maine**

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An earlier study of the inbreeding coefficients in about one-half of Maine communities revealed many static communities of major interest to human geneticists and demographers. This report will provide the inbreeding coefficients for virtually all communities in Maine. The estimates are derived by the surname-proportion method

which is based on the isonymy method. Data were taken from telephone books of the early 1960s. A simple relationship between the frequency of the most common surname and inbreeding coefficient was discovered. This relationship provides a quick but less accurate estimate of the inbreeding coefficient.

## **Detecting Carriers of Hemophilia**

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Data from four different laboratories are utilized to compare two methods for detecting the carrier state in classical hemophilia. One method uses a discriminant analysis and the second method utilizes a simple ratio between Factor VIII activity and Factor VIII antigen. Correcting for skewedness in the distributions, both methods give similar results.

Twenty-nine at risk females were tested for Factor VIII activity and Factor VIII antigen and the results of applying the two methods of carrier detection will be discussed.

## **Chloroform Toxicity in Male Mice**

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Genetic factors appear to control chloroform toxicity in mice and the degree of toxicity correlates with the amount of chloroform that accumulates in the kidney. Males of the inbred strain C57BL/6J have been shown to be resistant to chloroform; DBA/2J♂♂ are exceedingly sensitive, and the B6D2F<sub>1</sub> hybrids are intermediary in susceptibility. The amount of renal accumulation of <sup>14</sup>C-chloroform was measured in the BXD recombinant inbred lines derived from the cross of C57BL/6J and DBA/2J. The BXD lines appear to separate into two groups: a high uptake group and a low uptake group, suggesting that chloroform uptake is under the control of a single major gene.

## **IMMUNOLOGY**

### **A Procedure for Determining Possible Genetic Definitions from Immunogenetic Reaction Matrices**

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Blood group and histocompatibility antigens are frequently identified by their reactions with reagents or antisera. If a reagent is specific for a single antigen species the identification or definition of that antigen is straightforward and unambiguous. But reagents almost always cross-react with several distinct antigens and a single antigen may cross-react with several reagents. There are, therefore, usually many ways in which antigens or genes could be defined which would be consistent with the data represented in a reaction matrix. Linkage relations between genes, typing of individuals, frequency and recombination of genes, of course, all depend on the definitions of the genes and antigens involved. In practice, reagents are often assumed to be specific for a single antigen (which in turn corresponds to a single gene) simply because this does indeed give an unambiguous (although perhaps incorrect) definition and alternate possibilities are very complex. We give a procedure whereby antigens and genes can be defined which does not assume an absence of cross-reactivity. This procedure will be applied to get new and simpler interpretations of the human Rh and Ag blood group systems.

### **Antigenic Modulation in Pathogenic Trypanosomes**

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Antibodies can alter the distribution or expression of

surface antigens of eucaryotic cells. We are exploring whether such antigenic modulation potentiates the survival of pathogenic trypanosomes in an immunized host. Membrane ghost fractions were sedimented from homogenates of detergent-lysed, nuclease-treated *Trypanosoma brucei*. Washed ghosts contained antigens which protected immunized mice from subsequent infection with homologous parasites. IgG-enriched fractions of rabbit antisera to ghosts (I-Ig) contained antibodies which lysed homologous parasites in vitro at 37°. When I-Ig was diluted appropriately, cell lysis was only observed when active guinea pig complement (C') was added; fewer than 10% of the target cells were lysed by I-Ig in the absence of C'. Antibodies in I-Ig prepared 2-3 weeks after primary immunization could induce antigenic modulation in trypanosomes. Such I-Ig lysed more than 90% of target trypanosomes when added to cells at the same time as C' but lysed fewer than 10% of the cells when added to cells 15 minutes before C'. Cells incubated in normal Ig or in I-Ig at 0° for as long as an hour remained susceptible to immune cytotoxicity. Thus, preincubating trypanosomes in 2 week I-Ig at 37° renders the cells specifically resistant to subsequent lysis by C'. Such resistant cells are infectious for mice. *T. congolense* also undergoes antigenic modulation in response to anti-ghost I-Ig. The possible role of modulation in pathogenesis will be discussed.

#### Immunological Characterization of the Human Breast Cyst Progesterone Binding Protein (CPP)\*

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The human cyst fluid progesterone binding protein has been isolated by the combination of DEAE cellulose column chromatography and preparative polyacrylamide gel electrophoresis.

The evaluation of the degree of purification has been done by analytic polyacrylamide gel electrophoresis and by double diffusion and immunoelectrophoresis. The progesterone binding property has been detected by immunautoradiography. Cellular localization has been done by the enzyme-antibody-tagging method.

Results obtained show that: 1) The CPP is highly specific for this pathological fluid. 2) This protein has a strong and specific binding property for progesterone. 3) The protein is located in the cytoplasm of canalicular cells of the cyst. 4) Preliminary result indicate that this protein, which is normally absent in the human serum, is liberated and detectable in the serum of women with breast cancer. Therefore we propose the hypothesis that the liberation of this protein in the serum may be a marker for breast cancer.

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#### PHA Response: An Assay for Mouse T-Cell Response

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This paper includes a very brief review of the literature on phytohemagglutinin (PHA) response. The review will concentrate on papers which show characteristics of PHA stimulation.

A cell culture assay using PHA stimulation to study differences between old and young mouse spleen cells will be discussed.

Also included will be a description of the development of PHA assays in vitro for mouse spleen and lymph node cells using microplate cultures. The assay design is a two-dimensional matrix that allows the user to vary PHA dose and cell concentration concurrently. The matrix design is used to choose the optimal cell concentration and

PHA dose for maximum <sup>3</sup>H-thymidine uptake per cell. The resulting optimal conditions will be used to test lymph node, spleen, and peripheral blood cell response over a range of donor ages.

#### In Vitro Generation of Long-Term Cultures of Murine Tumor-Specific Cytotoxic T-Lymphocytes

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In vitro generation of murine lymphocytes, cytotoxic to syngeneic nonvirus-producing tumor cells has not previously been reported. Repeated mixed tumor-lymphocyte cultures (MTLC) have been effective in producing cytotoxic lymphocytes to a variety of target cells and this technique was applied to nonproducer models. Either DBA/2 or C57Bl/6 spleen cells were cultured with a mitomycin-treated allogeneic nonproducer leukemia cell at a lymphocyte:tumor cell ratio of 40:1. After five days of culture, cells were harvested and restimulated with the same allogeneic tumor cell for two additional days after which viable cells were tested for their cytotoxic reactivity against syngeneic tumor cells via <sup>51</sup>Cr release. Effector cells were cytotoxic to syngeneic virus producing and nonproducer leukemia cells as well as to syngeneic tumor cells whose cell surfaces were shown to lack viral antigens gp-71, p-30 and p-12. Effector cells were not cytotoxic to syngeneic thymus, lymph node or Con-A-stimulated spleen cells. Tumor-specific cytotoxic lymphocytes generated in this manner have been kept in continuous culture with the aid of a growth factor present in medium conditioned by Con-A-stimulated normal murine spleen cells. Cell lines grown in 40% conditioned medium continue to display syngeneic tumor-specific cytotoxic reactivity after more than six months in culture. Long-term cytotoxic cell lines are sensitive to lysis with antitheta serum and complement. The long-term growth of antigen pre-selected cytotoxic lymphocytes in vitro may allow for the generation of cytotoxic T-cells in sufficient numbers for immunotherapeutic trials in vivo.

#### In Vivo Relevance of the Requirement for Histocompatibility in Lymphocyte Cytotoxicity

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It has been observed that lymphocyte cytotoxicity in vitro of cells differing at non-major histocompatibility antigens requires compatibility at the major histocompatibility locus between the stimulating cells and the target cell. Two explanations have been proffered for this requirement: association of all minor antigens with major histocompatibility antigens or the necessity of two receptors, one for major histocompatibility antigens and one for "the other" antigen, for killer cell triggering (Zinkernagel, R. C. and Doherty, P. C., Nature, 248:701, 1974). The role of this requirement in vivo was investigated using allograft rejection. BALB/cByJ mice were given primary tail grafts of either C57BL/10Sn or B10.D2/nSn mice. C57BL and B10.D2 share minor histocompatibility antigens, but differ at the major histocompatibility locus. After rejection of the primary grafts, all mice received B10.D2 grafts. If the minor histocompatibility antigens were seen only in association with the major histocompatibility antigens (as suggested by either theory), then mice receiving primary grafts of C57BL should respond to the second graft of B10.D2 as a new antigen and reject this as a primary graft. It was observed, however, that animals given either primary graft demonstrated similar second set rejection of B10.D2. Although several explanations for this observation, including lack of restriction of helper cells and host macrophage processing, can be made while still maintaining the major histocompatibility restriction, it seems unlikely that this theory has in vivo relevance.

## **A mutation in the major histocompatibility complex of the mouse**

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Mutations occurring in the major histocompatibility complex (*H-2*) of the mouse are proving to be valuable tools for precise genetic definition of a region of Chromosome 17 that affects various phenomena associated with immune interactions. Such genetic definition will contribute towards understanding the basic mechanisms underlying immune responses in mammals including man.

A histocompatibility mutation was revealed by the rejection of skin-graft exchanges between (B10.RIII(71NS) × B10-M) F<sub>1</sub> hybrid individuals, and subsequent testing indicated that the mutation occurred in the *H-2<sup>f</sup>* haplotype of the B10.M congenic line. A line was developed (B10.M-*H-2<sup>fb</sup>*) that carried the mutation and differed from B10.M only at the mutated locus. Although skin grafts made between mice of the B10.M and B10.M-*H-2<sup>fb</sup>* lines were strongly rejected, reciprocal immunizations failed to induce detectable hemagglutinating or cytotoxic antibody.

Segregation analysis in a testcross of (B10.M-*H-2<sup>fb</sup>* × C57BL/10 Sn) × B10.M verified the *H-2* location of the mutation.

## **VIROLOGY**

### **Repair of Herpesvirus DNA**

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Herpes simplex virus type 1 strain MP was inactivated with increasing doses of agents that damage viral DNA. The damaging treatments employed included ultraviolet light, gamma radiation, a potent carcinogen; N-acetoxy-2-acetyl-aminofluorene and a bifunctional DNA cross-linking alkylating agent; nitrogen mustard. Virus survival was determined by plaque assay in a number of different human skin fibroblast cell strains derived from individuals with genetic diseases that are associated with decreased ability to repair certain kinds of DNA damage and predispose for the subsequent development of neoplasia. Analysis of survival curves indicate that ultraviolet and N-acetoxy-2-acetyl-aminofluorene-treated virus are repaired by the same pathway or pathways sharing a common rate-limiting step. The results also suggest that the phenomenon of host-cell reactivation may be utilized for the detection and/or selection of new mammalian DNA repair mutants.

### **The Effect of Pretreatment with 5-iodo-2'-deoxyuridine on the Replication of Varicella-Zoster Virus in Human Embryonic Lung Cells**

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Studies of the replication of human cytomegalovirus in cells pretreated with 5-iodo-2'-deoxyuridine (IUdR) have shown that virus production is enhanced with such pretreatment (St. Jeor and Rapp, J. Virol., 11:986, 1973). Experiments were designed to study the replication of another Herpesvirus, Varicella-Zoster (V-Z) Virus, in Human Embryonic Lung (HEL) Cells pretreated with IUdR. Three different strains of V-Z virus were compared: Ellen, RU-10, and a recently isolated wild type strain. Levels of 10 µg, 50 µg, and 100 µg/ml of IUdR were used. It was found 50 µg/ml of IUdR was the most effective concentration for the enhancement of virus production. Virus-infected HEL cells pretreated with 50 µg/ml IUdR showed a ten-fold increase in virus titer as compared to virus-infected untreated control HEL cells.

### **Clofibrate and the Role of Membrane Lipids in Herpesvirus Infectivity**

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The objective of our project is the elucidation of the role of membranes and specific membrane lipids in the infectivity of herpes simplex virus type 1 (HSV-1) in human cells in culture. The membrane systems of particular interest are those of the viral envelope and the nuclear envelope from which the viral are derived. In preliminary studies we demonstrated that the drug clofibrate dramatically inhibits the production of infectious HSV-1 in cultures of HEP-2 cells with little effect on host cell viability [Steinhart et al., Virology 70, 241, 1976]. Clofibrate is a hypolipidemic drug with seemingly diverse inhibitory effects on lipid metabolism in different systems. Our working hypothesis is that virus particles pick up altered nuclear membrane segments during envelopment in the presence of clofibrate, thus making the viruses defective in further infectivity. It is clear that a late maturation function of the virus is involved in the effect of clofibrate, since clofibrate is inhibitory when added as late as 7 hr postinfection. An extension of this project includes an examination of the productivity of HSV-1 in cells with genetically determined defects in lipid metabolism, cells we feel are analogous, at least in part, to wild type cells treated with a hypolipidemic drug.

### **Possible Viral and Genetic Interactions in Systemic Lupus Erythematosus**

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Two factors can be acknowledged as having established roles in the pathogenesis of systemic lupus erythematosus (SLE): (1) genetic components (not defined, as yet), and (2) immunologic processes mediating tissue inflammation and injury. From studies of the SLE-like illness of certain strains of mice, it is postulated that virus(es) constitute a third etiologic factor. Conceivably, these three components are interrelated: the same genes in the *H-2* region that regulate murine immune responses are also one facet of the host reaction to type-C viruses. I will emphasize recent data which support the thesis that genetic and viral factors analogously interact in the pathogenesis of the human disease.

### **Immunostimulation of Tumor Induction by Moloney Sarcoma Virus (MSV)**

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The immunostimulation theory postulates that a weak immune response to a tumor can stimulate rather than inhibit tumor growth. The role of immunostimulation in tumor induction by MSV was investigated *in vivo*. Since tumors induced by MSV are highly immunogenic, we tried to titrate the immune response to the tumor by immunizing mice with varying amounts of irradiated Moloney leukemia virus (MLV). If immunostimulation functions in this system, the weakly (low dose) immunized animals should demonstrate increased oncogenesis and the strongly (high dose) immunized should show decreased oncogenesis relative to non-immunized controls. After waiting for the primary antibody response to subside, all animals were challenged with a dose of MSV capable of inducing tumors in 50% of the animals. It was observed that animals receiving a high dose of MLV as immunogen developed no tumors. Those receiving low dose immunization, demonstrated an increased tumor incidence and a significantly decreased latent period compared to non-immunized controls. It was also found that if a 100% tumor producing dose of MSV was utilized for a challenge inoculum, a significantly decreased latent period was still observed in the weakly immunized mice. Although these results show that weak immunization can stimulate induction of tumors by MSV *in vivo*, the

mechanism is unknown. Tolerance or blocking phenomenon, as well as direct stimulation, may be responsible for this observation.

#### Attempts at Isolation of a Rabbit Type C RNA Virus

H. G. BEDIGIAN, R. R. FOX, and H. MEIER, The Jackson Laboratory, Bar Harbor, ME 04609

Rabbit cell cultures established from lymphosarcomatous tissues produce type C viral particles after induction with iododeoxyuridine. These particles band at a density of 1.16-1.18 g/ml and contain RNA-directed DNA polymerase activity (RDDP). The peak of polymerase activity was detected 2 days after induction and declines

rapidly thereafter. Viral RDDP and 70S RNA encapsulated in particular components that band in the density region of type C viruses was also demonstrated in rabbit tissues. That the RDDP detected in these tissues is distinct from the known cellular DNA polymerases is shown biochemically and biophysically. The purified RDDP has a molecular weight of approximately 70,000 daltons, showed a preference for  $Mn^{2+}$  as the divalent cation, transcribed heteropolymeric regions of the viral 70S RNA, and showed a preference for oligo (dG) • poly (rc) over the other template-primers used. To date, utilizing several mammalian cell lines, we have been unable to find a suitable host which will allow for the infection and propagation of the rabbit type-C RNA virus. (Supported by CTR and NCI).

#### "HEPATITIS" OUTBREAK — Continued from Page 241

families never mixed socially, never ate together or attend the same church. No one factor could have given all people illness simultaneously except perhaps a common commercial food source. Had this been the case, other physicians in the area should have seen hepatitis in their practices.

All bilirubins and SGOT's done on Dr. A's patients were run in his own office by a laboratory technician on an Ames colorimetric device. Although the technician was conscientious, there was no formal method by which she could compare her results to a standardized laboratory. We believe that the slightly high bilirubins in most patients could have been due to error in the machine, reagents used or in technique. Five bilirubin samples were drawn, split and run both by Dr. A's technician and a reliable laboratory standardized on a regular basis.

	Dr. A's lab.	Standard lab.
sample V	2.6	0.3
sample W	3.8	0.6
sample X	0.6	0.3
sample Y	2.0	0.2
sample Z	2.0	1.2

This comparison shows that Dr. A's bilirubins were in error.

It is becoming increasingly recognized that health professionals (dentists, physicians, laboratory technicians) may be involved in the spread of hepatitis to their patients.<sup>1,2</sup> Misdiagnosis of hepatitis may be another "iatrogenic" cause of

epidemics. Another recent "outbreak" in Arizona was traced to improper diagnosis using Ictotest® tablets which gave false-positive testing on urine.<sup>3</sup> In the Maine "outbreak," falsely elevated serum bilirubins and occasional false-positive urine urobilinogens were responsible. Since hepatitis may sometimes be subclinical, especially in children, it is tempting to diagnose the illness using only laboratory data, even if the patient is not ill. A cluster of cases diagnosed by a poorly standardized laboratory certainly raises the possibility of laboratory error. Physicians who maintain their personal laboratories should institute a regular check on results with a certified hospital laboratory.

In summary, a fictitious outbreak of hepatitis occurred in a Maine community, probably due to over-reliance on a laboratory test which was inaccurate; that one or two actual cases occurred cannot be ruled out, but certainly the majority did not represent hepatitis. The children and the two factory workers were all permitted to return to their schools or occupations.

#### ACKNOWLEDGMENT

We are grateful to Dr. Warren Kindig for running the split samples for bilirubin.

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# County Society Notes

## Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held on Tuesday, March 15, 1977 at The Ledges Inn, Wiscasset, Maine, with twenty-seven members and guests present.

The meeting was called to order at 8:20 p.m. by the President, Dr. Anthony J. Horstman. The minutes of the February meeting were read by the secretary and accepted as read.

There was no old business. Under new business, the secretary announced that Dr. Louis V. Dorogi is disabled and that his name will be submitted to the June meeting of the House of Delegates for election to Affiliate membership.

Dr. Horstman discussed the format of the April and May meetings. April will be devoted to House of Delegates business, while May will be Ladies Night, with a discussion of Alternates to Hospital Deliveries.

Several members discussed press distortion of medical socioeconomic issues.

Dr. Frank O. Avantaggio, Jr. introduced Dr. Ronald Carroll, a Portland oncologist, who spoke on Systems of Cancer Treatment.

GEORGE W. BOSTWICK, M.D., *Secretary*

## Hancock

A meeting of the Hancock County Medical Society was held at the Hilltop House in Ellsworth, Maine on Wednesday, April 6, 1977.

The meeting was called to order and the following items discussed by the President, Dr. John D. McIntyre:

1. Malpractice Law L.D. 727. There was a discussion of the recent hearing in Augusta, outlining the provisions of the law, and Dr. McIntyre encouraged members to support this legislation by contacting local legislators.

2. Joint Underwriting Association legislation and "right to die" legislation was also briefly mentioned.

3. A communication from Medical Care Development was read concerning the assignment of health personnel to various areas of "professional need" in the State. After discussion with members present, it was the general consensus that we have no concerns or problems regarding this need in our area and, thus, we see no need to support this project.

4. The problems facing the potential cutback or elimination of services at the Bangor Mental Health Institute were discussed. After presentations by several members and also by Dr. David Anderson, a motion was made by Dr. Morris A. Lambdin and seconded by Dr. Nancy Stewart that the Hancock County Medical Society support the continuation of the Bangor Mental Health Institute. This expression of support by the Society was approved unanimously.

5. Notice of the meeting of the Medical-Legal Liaison Committee workshop to be held at the Red Lion in Bangor on the 19th of April 1977 was given to the membership.

At this point, Dr. Bradley E. Brownlow, as speaker for the meeting, gave a discussion on the National Health Planning and Resources Development Act of 1974. He gave an outline of the structure of this act and how it is developing in the State of Maine. Following his very timely and stimulating address, there occurred a lively discussion amongst the group present. A motion was made by Dr. Lambdin and seconded by Dr. John R. Tyler that the Hancock County Medical Society express their support for the Maine Health Systems Agency and their plan for "Certificate of Need" legislation. The motion was passed by a close vote of six to five.

The meeting was then adjourned with agreement that the next meeting be established by the Executive Committee, preferably in late May or early June.

WILLIAM C. BROMLEY, M.D., *Secretary*

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## Acute Epiglottitis

(Management)

FREDERICK C. HOLLER, M.D., FACS

### ABSTRACT

**A brief description of the patho-physiology and clinical course of acute epiglottitis followed by a review of current methods of management.**

Acute epiglottitis is an acute inflammation of the epiglottic and aryepiglottic folds. It is a bacterial infection commonly due to *Haemophilus influenzae* Type B, although other organisms (Beta hemolytic strep, staphylococcus, etc.) have been implicated.

Epiglottitis is known for its devastatingly rapid course leading to upper airway obstruction, cardio-respiratory arrest and death, all within a few hours. Prompt, accurate diagnosis and appropriate treatment to insure an airway, are required.

Incidence is highest in the pre-school age child,<sup>1,2</sup> especially in the 1 to 2 year age group, although it can occur at any age, and has been reported in adults.<sup>3,4</sup> Males are more often affected than females<sup>1,2</sup> and there is no seasonal relationship.

Acute epiglottitis is often confused with subglottic croup with dire consequences. Epiglottitis is a bacterial inflammation involving chiefly the epiglottic and aryepiglottic folds, which are edematous and cherry red in appearance. Croup (acute laryngo-tracheobronchitis, subglottic laryngitis) is an inflammatory swelling of the submucous tissues in the conus elasticus (below the level of the true vocal cords) with crusting and exudate on the surface of the conus where loss of epithelium has occurred.<sup>5</sup> Respiratory distress with cyanosis are common with epiglottitis. Fever, stridor, dysphagia, drooling and excessive mucus are present in various combinations. The time from onset of symptoms to acute respiratory obstruction is usually only a matter of hours.

Subglottic croup is a viral illness. There is a history of antecedent upper respiratory infection with

nasal congestion. Hoarseness and a harsh "croupy cough" are characteristics. Inspiratory stridor and tachycardia are seen in both entities, however, in epiglottitis the respiratory rate is slower in relation to the pulse than would be expected because rapid forceful inspirations cause infolding of the epiglottis and aryepiglottic folds with further blockage of the airway. The patient prefers to sit up, lean forward, breathe slowly and drool and should not be forced to do otherwise. Some children will lay on their sides or in the prone position, tongue protruding with gurgling, stridulous respirations. The voice may be muffled but is not usually hoarse as in subglottic croup.

The diagnosis of epiglottitis may be established in one of three ways: oral exam with visualization of the swollen epiglottis, lateral neck x-ray or direct laryngoscopy.

If acute epiglottitis is suspected, examination must proceed expeditiously and with caution. Forcing the child to lay back may cause airway obstruction. Injudicious oral examination may stimulate the inflamed epiglottis (vagal reaction) and produce respiratory arrest, the so-called "tongue blade death."

Lateral x-rays of the neck and upper airway may reveal a swollen epiglottis but trips to and from the Radiology Department are fraught with delay and danger.<sup>6</sup> The patient should be accompanied by the primary physician.<sup>7</sup> Bass<sup>1</sup> points out that in his series most of the patients had been ill only 6 to 12 hours before requiring tracheotomy. The suddenness of the airway obstruction remains the hallmark of this disease.

Throat and blood cultures will delineate the offending organism later, but are of no help in immediate diagnosis. If on gentle oral examination an enlarged, edematous cherry red epiglottis is seen

rising at the base of the tongue, the diagnosis is established, but repeated injudicious examinations should be avoided. Direct laryngoscopy<sup>6,8</sup> will confirm the diagnosis in those instances where the epiglottis cannot be visualized. This should be done only in the appropriate setting of an operating room or intensive care unit where the necessary help and equipment are available. If respiratory obstruction occurs, one must be prepared for immediate placement of an endotracheal tube. However, this is not always possible through a deformed, swollen glottic inlet. Fearon<sup>9</sup> points out the importance of having a 3.5 mm. bronchoscope available for immediate insertion by one skilled in its use. Emergency tracheotomy may be necessary to establish the airway.

### MANAGEMENT

Three approaches to therapy have been proposed — tracheotomy, intubation, and medical. *Medical management* advocated by Strom and Jaffe<sup>10</sup> consists of steroid therapy (1 mg. per kg of Dexamethasone<sup>®</sup> for the first 5 kilograms and 1 milligram for each additional 5 kilograms of weight given intravenously initially and repeated at four hours and thereafter given every six hours). In addition, Ampicillin<sup>®</sup> and humidification are used. This conservative medical regime is given a two-hour trial period. If at the end of that time there is not significant improvement, then the patient is intubated. Tracheotomy is not done unless there is a problem with crusting in a small lumen tube or unless the patient cannot be extubated in 48-72 hours. This approach requires a greater investment of time and energy on the part of the managing physician. The protocol requires adequate personnel and skilled endoscopists. The endoscopist must remain at the bedside with all the essential equipment for the two-hour trial period, during which time the success or failure of the therapy is determined. Of the twelve cases reported, eight were successfully managed medically, two were intubated and two had tracheotomies. It was pointed out that the presence of cyanosis, exhaustion or severe sternal retraction precluded medical management alone.

*Intubation* — Over the past 5 years the pediatric, anesthesiology and otolaryngology literature have become replete with articles concerning the management of acute epiglottitis by nasal-tracheal intubation.<sup>2,11,12,13,14</sup> Advocates point out the short duration of the supra-glottic edema (usually less than 48 hours) making intubation management feasible. Intraoperative risks of tracheotomy, the possibility of tracheal stenosis at the site of tracheotomy or at the distal end of the tracheotomy tube, plus the problems of decannulation and the cosmetic deformity, are factors mitigating against tracheotomy. Also, pointed out is the fact that most tracheotomized patients have already had insertion of an endotracheal<sup>15</sup> tube and the hospital stay of the intubated patient, in several reports is shorter by 1 or 2

days.<sup>16,13</sup>

Complications of nasotracheal intubation include the problems of cardiac arrest during intubation and suctioning of the tube, accidental extubation, occlusion of the tube by crusted secretions and subglottic edema. Post extubation problems include subglottic stenosis, granuloma,<sup>12</sup> and laryngeal papilloma.<sup>14</sup> Nasotracheal tubes are more difficult to secure, more meticulous care is required of intubated patients with frequent suction and irrigation and it is often necessary to sedate the patients.

*Tracheotomy* — Until recently the mainstay of therapy in the treatment of acute epiglottitis has been insurance of an airway by prompt tracheotomy. At best intubation past an acutely inflamed, edematous epiglottis is difficult and in a few cases impossible. The presence of an endotracheal tube in an inflamed larynx acts as a foreign body and presents the definite hazard of laryngeal complications.<sup>17</sup> In some situations, an initial oral-tracheal tube has been passed and then under more controlled conditions was switched to the nasotracheal route. This would seem to double the hazard of immediate intubation complications. Schuller and Birch who favor intubation point out the mortality rate of tracheotomy (3.6%) versus the 0% mortality of intubation in their series. However, it would appear that the mortality associated with tracheotomy may be due to the hazardous circumstances associated with those procedures done at the bedside or in the emergency room on a patient who has already arrested and who could not be intubated. Rapkin<sup>8</sup> points out that in his series patients who were electively tracheotomized had no mortality.

### CONCLUSIONS

Tracheotomy, intubation and medical management are the options open in the care of acute epiglottitis. The establishment of an artificial airway via tracheotomy or intubation would still seem to be the surest, most widely accepted approach.

Medical management would seem to require a teaching center with house staff, and a pediatric intensive care unit with experienced personnel. The necessity that an expert endoscopist spend almost full time with the patient during a critical period of several hours, would also, mitigate against the practicality of the medical approach.

Elective tracheotomy and intubation seem about equally safe. Tracheotomy has the problem of operative complications, but once completed would seem to have fewer management difficulties and delayed complications. Endotracheal intubation avoids the cosmetic deformity of a neck scar and decreases the hospital stay by a day or two. As yet there is no overwhelming reason to favor one approach. Each physician must make a judgment based on his own capabilities and the resources of his hospital and medical community.

*Continued on Page 274*

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# PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

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*The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.*

*The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.*

## **The Advantages**

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy—and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

## **The Disadvantages**

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information

is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

## **The Solution**

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

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# Massive Intraperitoneal Bleeding From a Ruptured Hepatoma of the Liver

GEORGES S. ABOURJAILY, M.D., F.A.C.S.

It is not uncommon in any busy Emergency Room to encounter almost daily a patient with a hemoperitoneum due to trauma or a traffic accident. However, sudden intra-abdominal bleeding in a middle-aged male without a history of previous injury, constitutes a diagnostic and therapeutic challenge. The object of this paper is to present a rare case of massive intra-abdominal hemorrhage due to a sudden rupture of a liver tumor and its management.

## CASE REPORT

### HISTORY AND PHYSICAL EXAMINATION

A 54-year-old obese, married, steel inspector with an apparently completely negative medical and surgical history, presented at the Emergency Room on November 30th, 1975, with an acute abdomen and in a state of shock due to concealed blood loss. His family stated that he was in perfect health one hour prior to admission, when he suddenly felt weak, dizzy, and fell on his right side becoming unresponsive.

Upon physical examination, the patient appeared weak and thirsty. His face, skin, and extremities were pale and mottled. Vital signs revealed a blood pressure of 60/0, pulse 180/200/min. thready and weak, respiration rate 48. His lungs and heart were negative. His abdomen was obese, tense, and tender throughout. He was extremely rigid with guarding and rebound in the right upper quadrant and had a very strong KHER sign. He also had bilateral non-incarcerated inguinal-scrotal herniae. An abdominal tap in the right upper quadrant yielded non-clotting blood, and a portable x-ray of the abdomen revealed a hazy ground glass appearance. The patient was immediately resuscitated with copious amounts of colloids and crystalloids. He was typed and cross matched for eight units of whole blood and brought to the Operating Room under the impression of hemoperitoneum due to a ruptured abdominal or visceral aneurysm or deep laceration of the liver.

### THE OPERATIVE FINDING

Upon exploration, he was found to have roughly 2,500 cc. of fresh blood in his abdomen. He had a soft mass in the recto-sigmoid (possible diverticulosis) and the most pertinent finding was an actively bleeding, fairly deep laceration of the left lobe of the liver measuring roughly 7 cm. in depth with irregular and shaggy edges, extending between the gallbladder fossa and round ligament. (See Figure 1). Hemostasis was accomplished by the debridement of the laceration and suture ligation. He recovered satisfactorily. Final Path Report revealed a malignant hepatoma in the debrided specimen. (See Figure 2 a and b). Postoperatively, the patient went on to have a full medical and surgical work-up which was essentially negative including normal hepatic angiogram and serum alpha feto globulin. He was re-explored and underwent a cholecystectomy and partial left hepatectomy. (See Figure 3), with complete resection of his hepatoma.

He recovered from his second surgery very satisfactorily and was discharged ten days postoperatively in good condition to ambulatory care. Presently, nine month post-op, he is asymptomatic and assuming his regular work.

## DISCUSSION

Most cases of massive hemoperitoneal bleeding are due to trauma to the visceral or vascular struc-

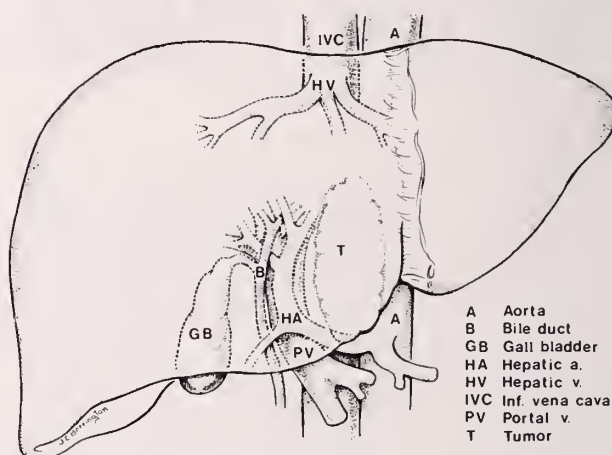


Fig. 1. Schematic Representation of the Tumor in Relation to Ductal and Vascular Structure of the Liver Hilum.

tures. In the hypertensive patient, a ruptured aortic or visceral aneurysm is the commonest cause. In the female, ectopic pregnancy and more recently, liver adenoma of hormonal cause, (contraceptives), appear with increasing frequency. Hemorrhagic pancreatitis or bleeding into a pseudopancreatic cyst are also possible causes. Occasionally, rupture of a hypernephroma or bleeding into a kidney cyst is seen, and finally, rupture of a liver tumor has to be kept in mind, although bleeding is not the most common sign of hepatoma. Balasegaram<sup>2</sup> reported 42 patients who presented with sudden rupture of a hepatoma. Swun J. Tant, Yu J.<sup>29</sup> noted 6 out of his 32 cases died of sudden intraperitoneal hemorrhage from spontaneous rupture of a hepatoma, and Adson<sup>1</sup> described two patients who experienced pain and hemorrhage as an initial sign of hepatoma.

## ETIOLOGY

Primary hepatoma is not common in the Western part of the world. It constitutes 0.4 to 0.72% of the malignant tumors; this is despite statistics indicating a rise in its frequency as pointed out by MacDonald and others.<sup>5,19,29</sup> It is insidious in onset and presents with advanced pre-existing disease of the liver, usually cirrhosis.<sup>2,5,10,13,15,17,20,29</sup> However, in the Far East, Africa, Japan, Malasia, Philippines, hepatoma constitutes 4% of all malignant lesions;<sup>2,17</sup> the causative factors remain unknown, although 60-80% of these cases has been reported in cirrhosis of the liver; aflatoxin has been implicated in liver cancer in Thailand and Kenya.<sup>2</sup> Mycotoxin seems to play a role and be an important factor in Malasian inhabitants.<sup>2</sup> Parasites in the liver on the other hand,

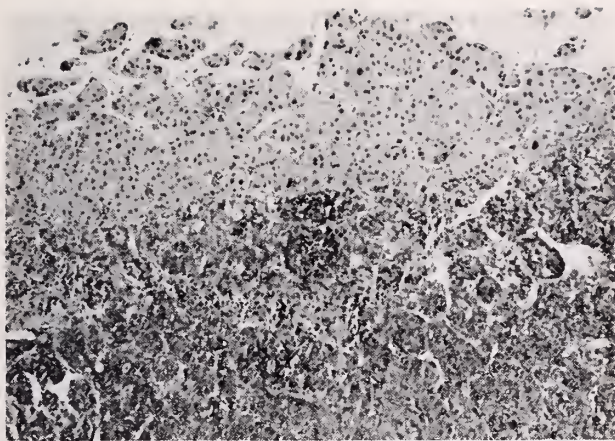


Fig. 2a. Microscopic section of the material debrided from the liver at the first operation. Note the sharp demarcation between the hepatoma and normal liver.

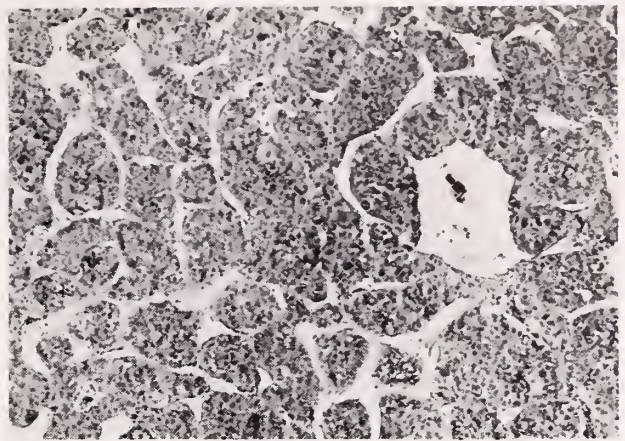


Fig. 2b. Photomicrograph showing the characteristic pattern of the hepatoma.

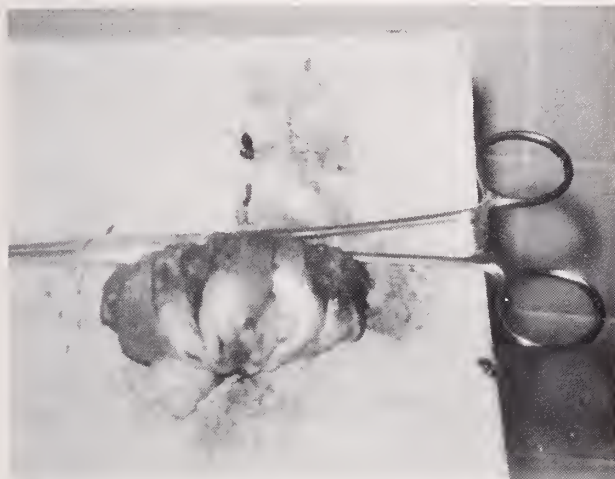


Fig. 3a

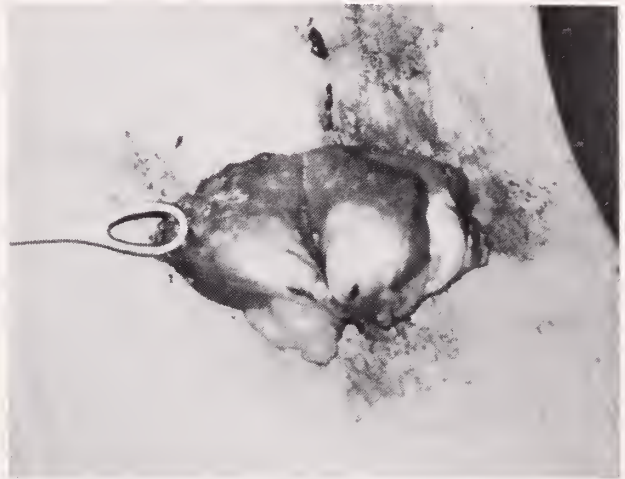


Fig. 3b

Fig. 3. Left Lobe of Liver including the resected Hepatoma in toto.

seems to have a close relationship to cancer of the liver in China, Japan, and the Philippines.<sup>17</sup> The link of viral hepatitis and the influence of diet is still unsettled.<sup>2</sup>

#### CLINICAL DIAGNOSIS

*Signs and Symptoms* — Primary hepatoma involves patients of all ages ranging from 6 months to 80 years with a peak incidence between the fifth and sixth decades.<sup>2,10,13,15,19</sup> The male-female ratio is roughly 4-1.<sup>15,19</sup> The most common clinical signs and symptoms are weight loss,<sup>2,15,19</sup> right upper quadrant pain,<sup>15,19</sup> intermittent fever;<sup>15</sup> palpable mass in the epigastrium or right upper quadrant is present in about one-half of the cases.<sup>15,19</sup> Hepatomegaly, icterus, and ascites occur later on as the disease progresses.<sup>1,2,15,29</sup> Spontaneous rupture and bleeding is common in this disease<sup>1,2,8,15,29</sup> and usually "tagged" with a poor prognosis.<sup>18</sup> Occasionally and rarely, symptoms of hypoglycemia with light-

headedness, sweating, tremor, syncope, and confusion has been reported.<sup>13</sup>

#### INVESTIGATION AND DIAGNOSIS

Liver function tests are not always abnormal; they are only positive in 40-50%.<sup>2,7,13,15</sup> Liver scan is negative unless the tumor has reached a fairly large size.<sup>1</sup> Liver needle biopsy could not be employed without hazard of serious complications such as bleeding and dissemination of a tumor,<sup>1,17</sup> and occasionally the diagnosis is often mistaken for a cirrhosis of the liver or fibrosis. Serum Alpha fetoglobulin with hydroxylase seems to be a constant and reliable measure, 94% yield positive with the exclusion of certain rare and unusual ovarian and testicular tumors.<sup>13</sup> Occasionally fasting hypoglycemia with 20-30 mg/ml has been noted in hepatoma.<sup>29</sup>

Finally, selective angiography is probably the most valuable, reliable, and helpful tool at the pre-

sent time, not only in demonstrating the neoplastic lesion of the liver, but also in delineating the circulation of the liver and reminding the operative surgeon of the numerous aberration of its vascular tree.

### TREATMENT

All forms of modality have been advocated in the treatment of a liver hepatoma from simple hepatic artery ligation<sup>3</sup> to partial portal vein ligation,<sup>14</sup> to complete hepatic dearterialization of the liver.<sup>3</sup>

Also chemotherapy has been used systemically as well as locally by means of infusion.<sup>28</sup> Nevertheless, the only cure of a hepatoma is certainly its removal by surgical resection. Here, I would like to emphasize that the surgeon should be familiar with the anatomical structure of the liver, the hospital should be able to offer not only an efficient operating room, but also full support from the Blood Bank and the skillful Postoperative Special Care Unit, anticipating the numerous metabolic problems which can occur after a major hepatic resection.

As far as the surgical technique, 25-35 years ago, surgery of the liver was primitive and limited to simple trauma and small superficial neoplasms. Packing of the lacerated liver and suture ligation and local application of thrombotic synthetic material such as Gelfoam® and Surgicel® was all that was done. It was not until the late 1940's that standardized surgical procedures were established, due largely to the pioneering and contributions of Honjo in 1949, Quattlebaum, Brunschwig, and Lerbot-Jacob in 1952, Feinberg, Lin, Goldberg, and Foster in the 1970's, Ochsner and Meyer reported a case alive 21 years later after segmentectomy for malignant tumor of the liver.

It is premature to predict the prognosis of this patient. The purpose here has been to emphasize and alert the physician facing a shocky patient in the Emergency Room with right upper quadrant pain, to the possibility of a ruptured hepatoma.

### SUMMARY OF THE CASE

A severe hemorrhage and a state of shock in a 54-year-old patient was caused by spontaneous rupture of a left lobe hepatoma which required prompt laparotomy; the lesion thought first to be of a traumatic laceration with possible hematoma of the liver, it was controlled initially with simple debridement and suture ligation. The Pathology report disclosed on final section, a left lobe hepatoma, necessitating, ten days later, left partial hepatectomy. The patient recovered uneventfully and was discharged home ten days postoperatively. Presently nine months after surgery, he remains asymptomatic.

### ADDENDUM

Since submitting my article for publication, the patient suddenly began to demonstrate signs of hepatic failure, requiring supportive therapy. He

declined hepatic perfusion or systemic Chemotherapy.

He expired fourteen months after surgery.

Post mortem exam was refused.

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# Debbie Won't Stop Biting Her Playmates: Behavior Modification in Family Medicine

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Having as a background the classical medical or psychoanalytic approach to problem behaviors, I have found as a family physician that my training was of little help when confronted with most of the maladjustive or deviant behavior of my patients. The majority of these people were not ill in a psychiatric sense. I did not deem it appropriate to involve them in an expensive, time-consuming, often unsuccessful psychotherapeutic program. My approach in the past has been that of a supportive therapist affording the person an element of relief through ventilation and concerned listening. However, I did not have many worthwhile suggestions for dealing with or changing the behavior. This behavior change was what the situation demanded, not an in-depth analytic approach. The "cure" was in reality a behavior change in an otherwise healthy well-adapted patient.

The family physician often has the first chance at correcting a problem behavior and the advice we give is often accepted as doctrine by our patients. Recently a mother brought her six-year-old child in to see me. She was concerned about temper tantrums. Over the past three years, on the advice of her previous physician, she had been placing the child in a hot bath following the tantrum and she wondered why this wasn't correcting the behavior.

Behavior modification has proven to be a useful tool on a daily basis to increase desired behavior or decrease undesirable behavior through an explanation of effective praise, ineffective scolding/spanking, criticism traps, proper use of punishment and avoidance of its possibly negative consequences. On approximately a monthly contact basis, I have been able to set up contingency programs for the following behaviors: for a parent to increase in-seat behavior at the dinner table, eliminate fecal soiling, temper tantrums, and decrease resistance to going to bed. One such behavior modification program and its results are described in this paper. It deals with a two-year-old child biting her playmates.

**PROBLEM:** Biting Playmates.

**DATA BASE:** Debbie D. is a two-year-old girl, who in early September of 1976, was placed in a baby-sitter's home during the day while her mother worked. This was the first time that she and her mother were separated for more than a few hours. Mrs. D. had not observed this biting behavior at her

home prior to this and had never seen it in any of her other children. The biting occurred one to four times a day over a three-week period in response to a playmate's refusal to relinquish a toy. The sitter, age thirty-five and a mother of three children, dealt with this biting in an inconsistent, often emotional way. At times she would separate the children, but keep Debbie with her as she did the cooking, sewing or housework and Debbie was allowed to participate in these activities in a helpful two-year-old way. Other times Debbie would be scolded or spanked. Debbie would occasionally be sent into another room to play by herself.

The mother's reaction to the reports of biting was consternation, anger, and guilt which often spilled into over-reaction to Debbie's other mild misbehaviors. She was often irritable with Debbie and called her a bad girl for biting her playmates.

In a psychoanalytic or psychodynamic sense, the biting behavior appeared to be an angry response at separation from the mother. The anger was misdirected at a peer, a less threatening individual. In a behavioral sense, the responses of the sitter and the mother were reinforcing the behavior. These reactions or consequences of Debbie's biting were explained to the mother as understandable in the circumstances, consistent with how most of us deal with our children, but inappropriate, self-defeating and confusing to Debbie.

## INTERVENTION STRATEGY

The behavior modification program set up with and agreed to by the mother and sitter employed the following features:

Counter-conditioning — Reinforcing a behavior incompatible with the biting

Time-Out — Removal from a situation in which she receives reinforcement

Negative Reinforcement — Removal of an aversive stimulus, i.e. the time-out chair

Positive Reinforcement — Rewards for no biting

### 1. Counter-Conditioning

Debbie was to be praised when playing constructively. The sitter would have to take the extra time required to observe Debbie and praise her, hug her, pat her on the head, etc. when she observed non-violent, cooperative play. Mrs. D. was also instructed to praise Debbie at home when playing well with her siblings.

### 2. Time-Out

Since the biting was dangerous, an aversive intervention had to be used immediately and a *time-out*

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chair was selected in an isolated area of an adjoining room. There Debbie could be observed and receive no reinforcing stimulation. Debbie was sent there without anger or undue attention by the sitter. Debbie was told that she was being sent there for biting and could return in ten minutes when she said she would not bite anyone.

### 3. Negative Reinforcement

Negative reinforcement is defined as the removal of an aversive situation. Debbie disliked the time-out chair and for the first three days had to be told repeatedly to stay in the chair. After three days, Debbie stayed in the chair for the ten minutes without coercion. Debbie was told that she could leave the chair when she said that she would not bite anyone. Thus, the chair was not a punishment in the sense that she could earn her release with a statement of positive intent at good behavior.

### 4. Positive Reinforcement

Mrs. D. had a collection of doll clothes in the attic trunk. It was explained to Debbie each day that she could go to the doll's chest and get a new dress for her doll if she did not bite anyone that day. Each afternoon, upon picking Debbie up at the sitter's, mother would receive a behavior report from the sitter in Debbie's presence. If she had not bitten anyone, then she got the reward as soon as they arrived home. Consistency was emphasized and no rewards were obtained if any biting, no matter how half-hearted, was noted during that day. After one week of no biting, the rewards were offered every other day for two weeks. Then the doll clothes were given once a week for a perfect week. After two weeks, the techniques were discontinued to see if the biting would recur.

## RESULTS

The described behavior modification program was started on October 4, 1976. The first week she was observed biting on three out of five days. The second and early part of the third week, only one out of five days. At the end of the third week and for the fourth week she was rewarded the second of two consecutive non-biting days. The fourth and fifth weeks no biting occurred and on the fifth week she was rewarded on Friday. However, on every non-biting day she did receive the very reinforcing approval of her mother and probably received other "hidden" rewards from a non-irritable, guilt-free mother, happier sitter, and more cooperative playmates. The reward system and time-out chair were withdrawn at the start of the sixth week and the biting behavior has not recurred in a follow-up of three weeks.

## DISCUSSION

Debbie's biting behavior was rapidly extinguished during this six-week program and has remained completely extinguished during the three-week follow-up. In a pure behavior modification study, the program is temporarily suspended after

successful elimination of the behavior to see if the problem behavior returns, thereby confirming that it was the behavior modification program and not some extraneous variables that caused the behavior change. Several factors inherent in the child, parent/sitter and the program may explain the extinction of the behavior.

The original biting behavior may not have been a well-established response to the situation (i.e., separation) since the situation was still relatively new. The child had in her repertoire of behavior the ability to cooperate and play well with her little friends and siblings. This cooperative behavior was easy to reinforce and was in direct competition with the undesirable behavior (counter-conditioning). Being, basically, a well-adapted little girl she may have responded as well to the intrinsic reinforcers: removal of scolding and spanking, the increased praise and attention for good behavior as she did to the extrinsic reinforcer — the doll clothes. Removal, then, of the aversive and negatively reinforcing "time-out" chair, and the positive reinforcing dolls' clothes reward would not reverse the behavior back to the biting state because the more subtle intrinsic reinforcers still existed. In addition, the biting might have reappeared if the experimental variables were withdrawn at week three when biting was still seen. I'm sure Mrs. D. would not have liked to see the biting return for the sake of this paper. Here we run into a conflict between the experimental purist and the parent/baby-sitter who want the behavior to stop, irrespective of how or why it stops.

The behavior we desire of Debbie is open to a great deal of reinforcement outside of the experiment. Polite, non-violent behavior which gets one what one wants can be taught to Debbie (and probably was) by mother/baby-sitter example, praising peers' cooperative play and sharing among her siblings. All of these are examples of modeling by "significant others" in Debbie's life. Thus, if Debbie learns a small measure of polite, cooperative non-violent behavior in the experiment, it can be reinforced in all of her areas of interpersonal relations outside of the sitter's home. This might be termed generalization of reinforcement.

This paper is an attempt to encourage the use of behavior modification techniques in a family physician's office through the analysis of certain well-defined behavioral principles in correcting a case of biting in a two-year-old child. Behavior modification has added a new dimension to my practice of family medicine. Suggested readings for physicians and patients on behavior modification in children can be found in the following paperbacks:

*Parents are Teachers* — Wesley C. Becker, Research Press.

*Living with Children* — Gerald R. Patterson, Ph.D., Research Press.

*Coping with Children's Misbehaviors* — Rudolph Dreikers, M.D., Hawthorne Books.

# Teenage Pregnancy in Maine†

## Health Problems and Nutritional Risk

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In Maine, the incidence of teenage pregnancies increased from 14% in 1959 to 19% of all pregnancies in 1973.<sup>1</sup> The trend in this State is representative of the trend that is occurring in the United States, and it is a source of concern to persons in many professions, especially those in the medical community.<sup>2</sup>

The adolescent pregnancy has been traditionally deemed a "high risk" pregnancy. The percent of low birth weight infants born to girls less than 17 years of age is reported to be twice as great as the rate of low birth weight infants born to women who are 25-29 years of age.<sup>1</sup> This ratio is significant because of the higher frequency of occurrence of neonatal deaths, poor infant development, mental retardation, cerebral palsy, and epilepsy in low birth weight infants, not to mention the higher cost of the increased care necessary during the neonatal period.<sup>1,3</sup> Prematurity, defined here as low birth weight, i.e., less than or equal to 2500 grams, is the direct or contributing cause in over half of the deaths that occur in the first month of life.<sup>4</sup> The death rate is thirty times greater among premature infants than among mature infants.<sup>4</sup>

Pregnancy may create a situation of critical nutritional stress for the teenage girl. This nutritional stress, alone, and in combination with other physiological, emotional, social, and economic problems increases the risks that the teenager will bear a low birth weight infant. Also, the teenage mother's health may be so adversely affected that she may not achieve a full recovery before her next pregnancy. Hence, her other children may also suffer because of the stress that was placed upon her during her first pregnancy.

Little is known about the state of the pregnant teenager in Maine. Investigations of nutritional problems on the public health level are almost nonexistent in the State.<sup>5</sup> The *United States Census* and the *Maine Vital Statistics* supply only limited information about pregnant teenagers in Maine.

Included in this study is an in-depth investigation of the most recent data concerning pregnant Maine teenagers and: low birth weight; illegitimacy; subsequent pregnancies; prenatal care; complications with pregnancy; congenital malformations; and educational services. Data pertaining to births to

teenagers Statewide, by county, by city, according to age, and with respect to birth order will be reported separately.

### METHODS

Current information about teenage pregnancies was requested from the Office of Vital Statistics, Department of Human Services. The number of births to mothers under age 20 was the only data that could be acquired.

The State Office of Computer Services was contacted to provide the most recent data available (1972, 1973, 1974) on all teenage pregnancies in Maine, according to the following characteristics: place of residence of mother; sex; out-of-wedlock; first born; under 2500 grams; congenital malformations; complications with pregnancy; no prenatal care; age of mother.

A statistical analysis of the data was completed utilizing: the Chi-squared test of association; Cramer's statistic (index for presenting the degree of relationship — complete independence to complete dependence — in any situation where Chi-square is utilized); and the Coefficient of Relative Variation (index to determine if relative changes are occurring, i.e., among counties making them more homogeneous or diverse with respect to each other). State data were compared to national data.

### RESULTS AND DISCUSSION

Total births in Maine have decreased from 1972-1974. There were 16,269 births in Maine in 1972, 15,638 in 1973, and 15,110 in 1974. Births to teenage mothers were 19.4% of the total births in 1972, 19.2% in 1973, and 18.0% in 1974.

Pregnant teenagers less than or equal to 17 years of age are those teenagers in most risk of bearing low birth weight (premature) infants.<sup>1</sup> In Maine, over one-third of all births to teenage mothers were from this "high risk" group. On a national scale, 24.1% of all infants weighing less than or equal to 2500 grams at birth were born to teenage mothers in 1971.<sup>6</sup> Maine figures for 1972 were similar showing 22.8% of all low birth weight infants born to adolescents.<sup>7</sup> From 1972-1974 combined, 7.8% of all low birth weight infants were born to teenage mothers. On a county basis (Table 1) the range of teenage-born premature infants was from 4.8% in Hancock County to 10.3% in Androscoggin County. Coefficients of relative variation showed homogeneity among counties over the three years.

Premature births to teenage mothers during 1972-1974 according to age are shown in Table 2.

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Due to added growth demands, poor eating habits, and lower levels of nutrition education the younger teens would be more suspect for producing low birth weight infants. For adolescents age 15 or younger, 10% of the births were premature. For those 16, 17, or 18 years of age approximately 8% of the births were premature, and the figure was 7% for nineteen-year-olds. Statistically, there was no significant difference in the number of low birth weight infants born to teenagers in these age groupings. Age of mother and birth weight were statistically independent at the State level during 1972, 1973, and 1974. No association between age of mother and

birth weight at the county level for 1972-1974 combined was found except for Kennebec County (Chi-square = 47.7), York County (Chi-square = 16.9), Cumberland County (Chi-square = 16.5), and Knox County (Chi-square = 16.1).

Age made very little difference in the percentage of all neonates born to teenage mothers that weighed between 2501 and 3500 grams. With respect to larger infants, a 19-year-old mother was more likely to give birth to an infant weighing greater than 3500 grams than was a 15-year-old mother.

From these data it is apparent that a younger teenage mother in Maine is *not* more at risk for prematurity than is an older teenage mother. Similar results have been found in other areas of the United States.<sup>3,8,9,10</sup>

Prematurity among teenage mothers was significant when legitimacy of birth was analyzed. Unwed teenage mothers gave birth to a higher proportion of low birth weight infants. Illegitimate infants comprised 28.1% of all neonates weighing less than or equal to 2500 grams, 23.8% of the infants that weighed between 2501 and 3500 grams, and 20.5% of the infants that weighed greater than 3500 grams (Table 3). Although the association between legitimacy and birth weight was statistically significant (Chi-square = 24.6;  $p < 0.05$ ), Cramer's index (0.05) showed the association to be small. However, it was shown that the unwed teenage mother is more at risk for prematurity.

The percentage of all illegitimate births to teenage mothers weighing less than or equal to 2500 grams according to age of mother and county is shown in Table 4. Comparison to weight data for all teenage mothers indicated comparable birth weights among teenage mothers less than or equal to 15 years of age regardless of legitimacy. The 18- and 19-year-old

TABLE 1

THE PERCENT OF ALL BIRTHS TO TEENAGE MOTHERS, WHERE BIRTH WEIGHT WAS LESS THAN OR EQUAL TO 2500 GRAMS, BY COUNTY, FOR 1972, 1973, AND 1974		
County	Total number of births where birth weight $\leq$ 2500 grams, three years combined	These births as a percentage of the total teenage births in each county %
Androscoggin	80	10.3
Sagadahoc	20	9.4
Piscataquis	16	9.3
Cumberland	129	9.2
York	71	8.2
Aroostook	75	7.8
Lincoln	14	7.8
Franklin	17	7.3
Washington	26	7.3
Kennebec	61	7.2
Somerset	33	7.1
Penobscot	75	6.8
Oxford	28	6.8
Waldo	17	6.0
Knox	17	5.8
Hancock	15	4.8
Maine Total	694	7.8

TABLE 2

THE PERCENT OF ALL BIRTHS TO TEENAGE MOTHERS THAT WEIGHED LESS THAN OR EQUAL TO 2500 GRAMS, BY AGE OF MOTHER AND BY COUNTY, FOR 1972, 1973, AND 1974

County	Age of Mother in Years					All Ages 15-19 %
	$\leq 15$ %	16 %	17 %	18 %	19 %	
Androscoggin	19.4	15.6	5.6	9.8	11.2	10.3
Sagadahoc	0.0	9.1	12.0	9.7	8.2	9.4
Piscataquis	11.1	15.0	13.3	9.6	8.2	9.3
Cumberland	13.6	13.4	4.5	10.2	8.5	9.2
York	5.4	3.3	13.9	8.1	7.1	8.2
Aroostook	6.1	9.3	8.4	8.4	7.1	7.8
Lincoln	0.0	0.0	15.6	8.7	4.5	7.8
Franklin	6.7	10.0	4.1	8.2	7.7	7.3
Washington	5.0	3.8	10.3	8.9	6.1	7.3
Kennebec	8.5	11.8	8.2	5.4	6.2	7.2
Somerset	13.0	9.5	10.4	4.3	6.1	7.1
Oxford	23.1	9.5	5.3	6.8	4.6	6.8
Penobscot	6.7	6.6	6.6	10.0	4.8	6.8
Waldo	0.0	0.0	9.6	5.8	7.1	6.0
Knox	27.3	2.6	12.2	3.0	4.2	5.8
Hancock	9.1	0.0	4.8	7.7	3.6	4.8
Maine Total	10.0	8.2	8.3	8.2	6.9	7.8

unwed mothers, however, had more premature infants and fewer infants weighing greater than 3500 grams than did all 18- and 19-year-old mothers. It could be speculated that the younger, unwed mothers usually remained at home and were being cared for by their parents. Such a situation might decrease the risk of prematurity due to illegitimacy. It is probable that the older, unwed teenage mothers were living independently of their parents, enhancing the risk of prematurity due to illegitimacy.

Subsequent pregnancies among teenagers is prevalent and of concern. There can be increased losses of nutrient reserves and further strain on overall health. Prematurity is a particular problem with repeat pregnancies, the rate being as high as 50%.<sup>2</sup> Nationally, 22% of births to adolescent mothers are second or greater in the birth order.<sup>6</sup> In Maine the figure is 17% (Table 5). Only a small percentage of births to mothers less than or equal to 16 years of age were not first born. However, in Oxford, Somerset, and Androscoggin Counties, mothers as young as 15 years gave birth to infants who were second or greater in the birth order. In Piscataquis County, 27% of all births to 17-year-old mothers were not first born. These are school age mothers, but it is unlikely that a girl so young with two or three children will continue her education.

Franklin, Washington, and Kennebec Counties contained the largest percentage of first born infants to teenage mothers. These three counties also had the highest percentage of births to mothers less than or equal to 17 years of age. Thus, in these three counties, it is probable that a greater percentage of the births occurring to the younger teenagers are first born infants.

There has been a decrease in teenage mothers not receiving prenatal care from 1972-1974 as shown in

Table 6. A decrease has also been found among all Maine mothers — 18.6% not receiving prenatal care in 1972 and 9.7% in 1973. Evidently more pregnant teenagers are seeking medical care upon discovery of their pregnancy. In addition, prenatal services probably became more available during the three years. Better reporting of whether or not prenatal care was received is also possible. Whatever the reasons, this trend for more prenatal care is important. It is through prenatal care that potential problems for the health of the mother and child are detected and treated.

There were 1,121 pregnant teenagers who did not receive prenatal care from 1972-1974. In most counties, less than 10% of the births were from mothers

TABLE 3

THE PERCENT OF ALL BIRTHS TO TEENAGE MOTHERS, GROUPED ACCORDING TO WEIGHT, THAT WERE ILLEGITIMATE, BY COUNTY, FOR 1972, 1973, AND 1974

County	Birth Weight in Grams		
	≤2500 %	2501-3500 %	≥3501 %
Knox	52.9	19.0	15.4
Lincoln	50.0	22.0	14.9
Cumberland	34.9	28.2	24.4
Hancock	33.3	28.5	19.4
Somerset	33.3	25.8	26.1
Oxford	32.1	21.6	22.3
Washington	30.8	26.2	26.8
Kennebec	29.5	23.7	25.9
Franklin	29.4	21.0	15.3
Androscoggin	27.5	21.8	18.6
Aroostook	26.7	23.6	18.9
Penobscot	22.7	25.8	17.6
Sagadahoc	20.0	18.3	23.7
Piscataquis	18.8	17.3	32.8
Waldo	17.6	20.8	22.9
York	16.9	20.9	11.6
Maine Total	28.5	23.8	20.5

TABLE 4

THE PERCENT OF ALL ILLEGITIMATE BIRTHS TO TEENAGE MOTHERS THAT WEIGHED LESS THAN OR EQUAL TO 2500 GRAMS, BY AGE OF MOTHER AND BY COUNTY, FOR 1972, 1973, AND 1974

County	Age of Mother in Years					All Ages 15-19 %
	≤15 %	16 %	17 %	18 %	19 %	
Lincoln	0.0	0.0	27.3	27.3	12.5	18.4
Knox	42.9	9.1	25.0	0.0	16.7	16.1
Androscoggin	20.0	16.7	4.9	21.4	7.7	13.2
Cumberland	10.2	17.2	7.9	12.0	11.8	11.6
Franklin	0.0	11.1	7.7	20.0	9.1	10.9
Oxford	10.0	5.6	10.5	4.8	15.4	9.6
Aroostook	4.8	12.5	9.4	9.4	9.3	9.4
Somerset	16.7	15.4	4.2	6.4	8.3	9.0
Kennebec	3.6	16.2	9.4	6.0	5.3	8.7
Sagadahoc	0.0	28.6	0.0	7.7	8.3	8.5
Washington	12.5	4.4	18.2	0.0	11.8	8.4
York	4.5	3.4	16.1	5.1	13.6	8.4
Piscataquis	0.0	11.1	0.0	11.1	7.7	7.0
Hancock	0.0	0.0	5.6	9.5	11.1	6.5
Penobscot	10.0	4.4	3.6	9.4	7.1	6.7
Waldo	0.0	0.0	0.0	10.5	9.1	4.8
Maine Total	10.0	10.5	8.7	9.8	9.5	9.7

TABLE 5

THE PERCENT OF ALL BIRTHS TO TEENAGE MOTHERS THAT WERE NOT FIRST BORN, BY AGE OF MOTHER AND COUNTY, 1972, 1973, AND 1974

County	Age of Mother in Years					All Ages 15-19 %
	≤15	16	17	18	19	
	%	%	%	%	%	
Knox	0.0	2.6	8.2	24.2	32.3	20.5
Washington	0.0	5.7	10.3	16.8	25.4	19.8
Somerset	4.4	6.2	10.4	17.3	30.3	18.7
Hancock	0.0	5.7	6.4	18.7	30.9	18.4
Piscataquis	0.0	0.0	26.7	17.3	23.0	18.0
Waldo	0.0	0.0	15.4	19.8	25.2	17.7
York	0.0	10.9	9.6	19.7	23.2	17.4
Lincoln	0.0	6.7	8.9	17.4	26.9	17.2
Androscoggin	3.2	5.2	10.6	15.0	26.5	16.7
Cumberland	0.0	6.0	8.6	18.2	24.6	16.4
Oxford	11.5	7.7	7.7	19.4	22.2	16.3
Sagadahoc	0.0	0.0	16.0	21.0	17.8	16.0
Aroostook	0.0	4.0	11.2	13.9	22.8	15.8
Penobscot	0.0	1.6	7.8	16.2	24.8	15.7
Kennebec	0.0	4.9	6.0	17.2	26.6	15.4
Franklin	0.0	10.0	6.1	15.1	23.1	13.8
Maine Total	1.2	5.1	9.5	17.4	25.1	16.6

TABLE 6

THE PERCENT OF ALL BIRTHS TO TEENAGE MOTHERS, WHERE THE MOTHER DID NOT RECEIVE PRENATAL CARE, BY COUNTY AND BY YEAR

County	Year		
	1972	1973	1974
	%	%	%
Oxford	39.3	46.8	30.2
Aroostook	40.9	39.1	21.0
Cumberland	46.2	12.3	5.4
Knox	34.9	14.5	5.2
Lincoln	8.5	8.3	8.2
Waldo	12.4	3.7	0.0
Somerset	6.3	6.6	4.5
Penobscot	7.6	5.1	4.1
Sagadahoc	11.4	3.5	0.0
Kennebec	4.5	3.6	5.1
York	6.9	3.1	2.6
Franklin	3.3	6.6	1.6
Washington	5.1	2.4	3.5
Androscoggin	1.1	2.3	3.7
Hancock	0.9	1.9	2.0
Piscataquis	3.1	0.0	0.0
Maine Total	18.5	11.6	6.7

not receiving prenatal care. Exceptions were Oxford (39%), Aroostook (35%), Cumberland (23%), and Knox (19%). Simply, the unavailability of medical services, such as private physicians and prenatal clinics, would explain the situation in Oxford and Aroostook Counties. In Cumberland and Knox Counties, it is possible that the existing services were not sufficient to meet all the needs and demands for prenatal care. The coefficients of relative variation indicated county homogeneity with respect to prenatal care. Thus, the trend for increased prenatal care among pregnant teenagers was occurring at the same rate in all the counties.

Over the three-year period, a total of 425 teenage mothers experienced complications with their preg-

TABLE 7

THE PERCENT OF ALL BIRTHS TO TEENAGE MOTHERS, WHERE THERE WERE COMPLICATIONS WITH THE PREGNANCY, BY COUNTY, FOR 1972, 1973, AND 1974

County	Total number of births where teenage mother experienced complications with pregnancy, three years combined	These births as a percentage of the total teenage births in each county
		%
Knox	48	16.4
Washington	35	9.8
Hancock	24	7.8
Sagadahoc	15	7.0
Cumberland	95	6.7
Lincoln	12	6.7
Waldo	17	6.0
Kennebec	36	4.3
Piscataquis	7	4.1
Androscoggin	30	3.8
York	31	3.6
Franklin	7	3.0
Aroostook	25	2.6
Somerset	12	2.6
Penobscot	24	2.2
Oxford	7	1.7
Maine Total	425	4.8

nancies (Table 7). This represented 4.8% of all births to teenage mothers. Most complications with pregnancy were found in Knox County. The coefficients of relative variation (0.4, 1972; 0.7, 1973; 0.6, 1974) showed relative changes occurring among the counties, and these changes were towards more variation rather than homogeneity. An explanation for the variation would be that from 1972 to 1974 there were increases in the number and percentage of teenagers experiencing complications with pregnancy in Aroostook, Cumberland, Knox and Washington Counties. The other counties remained relatively the same over the three-year period.

TABLE 8

THE PERCENT OF ALL BIRTHS TO TEENAGE MOTHERS,  
WHERE CONGENITAL MALFORMATIONS WERE PRESENT,  
BY COUNTY, FOR 1972, 1973, AND 1974

County	Total number of births where congenital mal- formations were present, three years combined	These births as a percentage of the total teenage births in each county %
Sagadahoc	7	3.3
Washington	10	2.8
Knox	7	2.4
Piscataquis	4	2.3
Hancock	6	1.9
Cumberland	25	1.8
York	15	1.7
Aroostook	16	1.7
Lincoln	3	1.7
Penobscot	17	1.6
Somerset	6	1.3
Androscoggin	6	0.8
Oxford	3	0.7
Waldo	2	0.7
Kennebec	6	0.7
Franklin	1	0.4
Maine Total	134	1.5

Aroostook, Cumberland, and Knox Counties were also those in which a large percentage of teenagers were not receiving prenatal care. It is possible that a teenager who has not received prenatal care is more susceptible to complications with pregnancy. It should be noted that as the percentage of teenagers receiving prenatal care increased in these counties, so did the percentage of teenagers who experienced complications with pregnancy. Better reporting of prenatal care and complications with pregnancy may partially explain this unusual trend.

In Maine, in 1972 and 1973, there were congenital malformations associated with 1.6% of the births to mothers of all ages.<sup>7,11</sup> Congenital malformations were present in 1.5% of all infants born to teenage mothers for 1972, 1973, and 1974 (Table 8). There were no differences in the occurrence of congenital malformations among infants born to teenage mothers as compared with those born to all mothers. The coefficients of relative variation indicated few relative changes among the counties over the three years.

Mothers less than or equal to 17 years of age gave birth to approximately one-third of the neonates born to teenagers. These mothers are still of school age, yet educational services in this State for such mothers are practically nonexistent. The Maine Children's Home for Little Wanderers and the Waterville School District operate the only accredited school for pregnant teenagers in the State. It is appropriate that the school is in Kennebec County, as the largest number and the largest percentage of teenage mothers in that county were 17 years of age or younger. It could be argued, on the basis of numbers of teenage pregnancies and geographical loca-

tion, that there should be educational services for school age mothers in Cumberland, Penobscot, Aroostook, Androscoggin, and Somerset Counties. An educational program would also be of value in Farmington. Forty percent of all teenage mothers in Franklin County were 17 years of age or younger and the majority lived within a 25-mile radius of Farmington. Educational services are also needed in Washington County, but the pregnant teenagers there are dispersed, and it would be difficult to operate just one, central program. Washington and Somerset Counties had high incidences of repeat pregnancies which occur most often among those teenagers who have left school. Vocational counseling and education are a major means of preventing subsequent pregnancies.<sup>12,13</sup> This would be further justification for establishing educational services for pregnant teenagers in Washington and Somerset Counties.

The counties in Maine were relatively homogeneous with respect to changes in the incidence of teenage pregnancy and to the other characteristics studied from 1972-1974. This finding indicates that, once external variables such as population, income, urban versus rural setting, etc. have been accounted for, the trends in these characteristics are the same for most counties.

Every pregnant teenager deserves medical and nutritional consideration. Many are likely to be at risk, especially those who are less than or equal to 15 years of age and have not yet completed their own physical growth. When the burden of pregnancy is added, a health hazard is created that may adversely affect both the mother's and infant's health for many years. The nutritional status of the mother is an important determinant of reproductive efficiency.<sup>8,14</sup> In all social strata, teenage girls have the least favorable food intakes of all age groups,<sup>8,14,15,16,17</sup> and it is probable that their nutritional status levels are not optimal for pregnancy. Environmental factors, such as stress that occurs because of an inappropriate pregnancy, may further increase the teenage girl's requirements for nutrients and thus create an even greater strain on her nutritional health.<sup>9</sup> Also, subsequent pregnancies during the teen years might significantly deplete nutrient reserves.

In Maine, pregnant teenagers are in need of medical care, with prenatal and nutritional components; educational programs; and family planning services. It is probable that the costs of these preventative measures would be far less than the welfare and acute care costs that may occur if these services are not provided.

#### SUMMARY

Demographic data of teenage pregnancies in Maine were analyzed for 1972, 1973, and 1974. Birth weight was not statistically lower among younger teenagers. Low birth weight babies were, however,

more prevalent among unwed teenage mothers. Subsequent pregnancies were found among mothers as young as 15 years in Somerset, Oxford, and Androscoggin Counties, and more than one fourth of all births to 17-year-old mothers in Piscataquis County were not first born. A trend for more prenatal care for Maine teenagers throughout the State was found. There was some county variation with respect to mothers experiencing complications with pregnancy. Congenital malformations were not more prevalent among teenage mothers. Educational programs for pregnant teenagers in Maine are warranted.

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# A Test of Consumer Contribution to Small Area Variations in Health Care Delivery

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Variations in use of medical services have been documented across nations and states and between populations living in neighboring communities. Among neighboring medical service areas, the differences are often more extensive than among larger, politically defined areas. Lembcke's finding of variations among neighboring medical care systems<sup>1</sup> have been reported in Hanover, West Germany;<sup>2</sup> in Saskatchewan;<sup>3</sup> in Kansas;<sup>4</sup> Vermont;<sup>5,6</sup> and Maine.<sup>7,8</sup> Among Hospital Service Areas in Vermont and Maine, rates for medical admissions, diagnostic procedures, expenditures for hospitals and reimbursements under the Medicare Part B program are as varied as for surgical procedures.<sup>5,8,9</sup>

Published evidence suggests that variations in the amount, type and cost of medical care relate to the characteristics of the suppliers of medical care (the physicians and hospitals)<sup>4,5</sup> and the pattern of use of specific procedures suggest differences in physician decisions in defining need and belief in technology contribute to variations.<sup>3,7,10,11,12</sup> The assertion that supply factors bear the major responsibility for variations in utilization among neighboring areas rests on the assumption that the populations are (more or less) similar in health needs or behavior in purchasing care. However, with the exception of the rate of having health insurance, which was controlled for in the Kansas study, no direct evidence has been published to show that the distribution of individual determinants of demand for health care are, in fact, similar.

It should be noted that it is critical to directly evaluate the contribution of consumer characteristics to small area differences in rates of expenditure and utilization. In the face of mounting evidence that health care facilities and personnel determine per capita variations in costs and utilization among neighboring health care markets, the dominant strategies for affecting health care use continue to be aimed at the patient's own decision — increasing his ability to pay for health care, or building in deductibles to discourage individuals from unnecessary use of physicians or hospitals. The efficacy of such approaches rests on the assumption that patients in the aggregate control, or at least significantly affect,

consumption rates in the local market in which they participate.

There are a number of factors that influence the medical care that individuals receive: their income, their education, their age, their morbidity, whether or not they have health insurance, their access to physicians. This paper addresses the question of whether or not average differences in these characteristics that affect individual behavior can account for between-area differences in the amount of medical care received.

## METHOD

Areas in Vermont have previously been shown to vary extensively in the quantity and cost of health care delivered. When a state-wide health survey was designed, six areas within the state were selected to be over-sampled so that reliable estimates could be made of population characteristics for each area.

The six areas chosen include two where the residents most often went to a major university hospital, two where they used a local hospital with more than 100 beds, and two where they used a hospital with fewer than 100 beds. As Table 1 shows, in all cases over 60% of resident hospitalizations are in the main local hospital. The six selected areas varied considerably in their hospital admission rates, their rates of surgery and the expenditure for health care as reflected in Medicare Part B payments. Age-adjusted admission rates vary from a low of 127 to 220 patients per 1,000 population. The Hospital Service Areas served principally by smaller hospitals are strikingly different. The two areas served principally by university hospitals show some difference with Area 1, 14% higher than Area 2; however, in the area with the lower rate, a greater portion of local residents are hospitalized in non-university hospitals. Use of surgery shows a similar pattern of variations.

Per capita reimbursements under the Medicare Part B program differ: enrollees in Area 1 receive 1.8 times the amount received by those in Area 6. The differences do not relate strictly to size or function of the principal hospital. Residents in Area 1 (\$162 per enrollee) and Area 2 (\$116 per enrollee) receive most of their care in university hospitals; Area 5 (\$140 per enrollee) and Area 6 (\$92 per enrollee) are each served by a smaller hospital.

The detailed methodology for these calculations has been described in previous articles, as well as the associations between these variations and such

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TABLE 1

USE OF MEDICAL CARE IN SIX SAMPLED HOSPITAL SERVICE AREAS						
	Area 1	Area 2	Area 3	Area 4	Area 5	Area 6
Patient Hospitalized in:						
Community Hospital <100 Beds	3.9	31.8	3.6	3.3	75.4	66.3
Community Hospital >100 Beds	18.2	4.4	80.0	90.3	8.5	3.8
University Hospitals	77.9	63.8	16.4	6.4	16.1	29.9
Hospitalization Rate (Discharges per 1,000, 1973)*	145	127	160	173	220	132
Surgery Rate (Discharges per 1,000, 1973)*	58	54	58	66	80	49
Medicare Part B (\$ Reimbursement Per Enrolled, 1972)	\$162	116	141	121	141	92
Number of Local Hospitals	2	2	1	1	1	1

\*Age-adjusted to Vermont population

TABLE 2

CHARACTERISTICS OF SAMPLED VERMONT HOSPITAL SERVICE AREAS							
	Area 1	Area 2	Area 3	Area 4	Area 5	Area 6	State- Wide
Interviews Completed	326	258	283	262	280	245	2,190
Number of Adults in Interviewed Households	649	474	551	525	541	478	4,292
Number of Individuals in Interviewed Households	986	704	807	853	858	765	6,681

supply characteristics as the per capita number and specialties of physicians serving the areas and the per capita bed supply of hospitals.<sup>5</sup>

The survey questionnaire was designed by a research team at the National Center for Health Services Research and Development for use in different sections of the United States as part of the federally funded Experimental Health System Delivery Program. Vermont was a program participant when this study was carried out. The survey instrument dealt in a standard fashion with demographic information and obtained data on service utilization and morbidity. Options for additional questions permitted Vermont investigators to inquire into insurance status and use of certain ambulatory services.

The interviews were taken (February through March, 1973) by telephone wherever possible (about 70%) and by personal interview when a telephone call could not be completed. At least 6 calls were made to locate difficult-to-reach respondents. Telephone interviews were conducted by the regular, experienced SRP<sup>†</sup> field staff. A specially trained staff of interviewers in Vermont, supervised by SRP, carried out the personal interviews. At each selected housing unit, the person who "knows most about the health of the family" reported for him or herself and for other related persons living there.

<sup>†</sup>The sample design and field work for the household survey was the responsibility of the Survey Research Program (SRP), a facility of the University of Massachusetts and the Joint Center for Urban Studies of the Massachusetts Institute of Technology and Harvard University.

Proxy information was not taken regarding non-relatives in the household; a separate interview was conducted with each unrelated individual in a household. The sample yielded about 2,300 housing units. The response rate was 87%. The number of households, adults and individuals for whom information was obtained in each area are given in Table 2.

The statistical methods of assessing variations in the case of the household survey are based on Chi-Square distribution. The null hypothesis postulates equality between expected proportions of individuals with a given attribute in each area and is rejected if any area differs from the others ( $P \leq .05$ ). For attributes for which the null hypothesis is rejected, their association with hospital utilization and expenditures is tested by partitioning the Chi-Square into a linear trend component related to the utilization variable and a residual component.

## RESULTS

### Population characteristics

In contrast to their use of hospital care or reimbursements, the populations are homogeneous on most factors that relate to individual use of care (Table 3). The areas are similar in racial composition, in number of adults born in Vermont and in the percent of adults who have lived 20 years or more in their current areas of residence. High and low hospital use areas have rather similar portions of adults who were born on a farm; the high and the low expenditures areas have about the same percentage

TABLE 3

## CHARACTERISTICS OF POPULATIONS LIVING IN SIX SAMPLED HOSPITAL SERVICE AREAS

	Area 1	Area 2	Area 3	Area 4	Area 5	Area 6	Statistical Comparison Among Areas
Socio-demographic Characteristics of Adults:							
Percent with One or More Years of College	35	35	31	21	26	33	.05
Percent White	98	99	99	99	97	98	N.S.
Percent Raised on Farm	31	33	35	34	50	42	.001 <sup>2</sup>
Percent Vermont or New Hampshire Born	66	60	68	64	61	59	.05 <sup>2</sup>
Percent Living in Area More Than 20 Years	47	49	47	57	47	47	N.S.
Household Economic Characteristics:							
Percent Below Poverty Level	21	19	20	21	23	20	N.S.
Percent with Health Insurance <sup>1</sup>	83	84	83	82	84	84	N.S.
Percent of Insurance Policies Blue Cross	51	54	47	47	54	50	N.S.
Households with Regular Place of Physician Care	98	99	98	98	99	97	N.S.
Illness Level:							
Percent with Any Restricted Days in Last 2 Weeks for Chronic Condition	5	5	6	7	4	5	N.S.
Percent with Chronic Condition	26	28	29	28	23	23	.05 <sup>2</sup>
Percent with More Than 2 Weeks of Bed Days in Last Year	6	6	5	7	5	4	N.S.

<sup>1</sup>Excluding Medicare and Medicaid.<sup>2</sup>Linear Trend Component of Chi-Square Statistic related to rank on expenditures and utilization of hospitals not significant.

TABLE 4

## RESIDENT ACCESS TO PHYSICIANS AND HEALTH SCREENING SERVICES IN SIX SAMPLED HOSPITAL SERVICE AREAS

	Area 1	Area 2	Area 3	Area 4	Area 5	Area 6	Statistical Comparison Among Areas
Health Services							
Percent of Population With Physician Contact Within Year Preceding Interview	77.3	76.1	74.2	70.9	73.4	72.6	.001 <sup>2</sup>
Percent of Population With Episode of Illness Contacting Physician Within 2 Weeks of Interview	29.3	29.8	34.1	34.4	26.1	30.2	N.S.
Percent of Females 18 Years or Older Receiving One or More Papanicolaou Tests <sup>1</sup> Within Year Preceding Interview	59.5	52.2	56.5	49.8	54.8	63.2	N.S.

<sup>1</sup>Within 1 year of interview.<sup>2</sup>Linear trend component of Chi-Square significant  $P < .001$  for hospital utilization; non-significant for Medicare Part B expenditures.

of persons with some higher education.

Residents of the different areas tend to have similar economic circumstances. There is little difference in percent of population below poverty level. Between 83% and 85% of area residents have health insurance. Between 47% and 54% of insured households have purchased Blue Cross insurance. Very nearly all households have a regular place of physician care. In contrast to large urban areas, emergency rooms play almost no role in providing routine care. Private doctors' offices are the most common places where primary care is received.

An estimate of chronic conditions was obtained by asking household members if during the last year they had "any health problem or illness" for a period of three months or more. While statistical differences exist between areas in chronic illness

levels, they are not large and do not relate to relative consumption of hospital care. Two other measures of illness level (restricted activity within two weeks of interview and percent of population with more than two weeks of illness which confined an individual to bed during the previous year) showed no difference between areas.

#### Patient initiated demand for service

The similarities across the areas in availability of a regular place of physician care and in socio-demographic, economic, and illness factors which relate at an individual level to use of health services suggest that, on the average, residents of the area will not differ in their own ability, need or interest in consuming medical care. Their rates of contact with physicians bear out this expectation (Table 4). On an annual basis, between 71% and 77% of persons see a

TABLE 5

ANTICIPATED ROLE OF CONSUMERS IN CHOICE OF HOSPITAL  
(By Level of Education)

	Educational Level		
	<i>Less Than High School</i> <i>N = 688</i>	<i>High School Graduate</i> <i>N = 796</i>	<i>One or More Years of College</i> <i>N = 764</i>
<i>Respondent Expectation About Role in Selecting a Hospital</i>			
Percent Who Would:			
Rely on Own Judgment	24	18	16
Rely on Physician	66	70	60
Make a Joint Decision With Physician	10	12	25

physician. While these differences are statistically significant, they are not large and are unrelated to Medicare Part B reimbursements. The linear trend component of the Chi-Square is significant for the relationship with discharge rate: areas with lower contact rates tend to have higher hospitalization rates. The difference is small, and if there is a significance it is opposite that expected if lower rates of use of hospital result from lower rates of contact with physicians.

Behavior in seeking care among those who are ill also appears similar: for an episode of illness that occurred within two weeks of interview (defined as one or more disability days), about the same portion of persons who were ill saw a physician in the different areas. No differences were detected between areas in use of cervical tests for cancer.

Finally, we might present one further table that bears not on the between-area variations *per se*, but on the basic question of the extent to which patients control the health care they receive. In Vermont, as elsewhere, the decision of which hospital one uses has a marked impact on the cost of service. It is possible to think that patients choose their hospital; and no doubt some do. However, when we asked people directly how they would decide on a hospital, the overwhelming response was that they would rely on their physician's judgment (Table 5).

### DISCUSSION

Our study does not support the hypothesis that the variations across neighboring communities are explained by consumer behavior. The personal resources of individuals and families appear to be the same in areas of high and areas of low use of hospitals: the populations-at-risk are similar in extent and variety of insurance coverage, portion below poverty, racial background and in rates of reported illnesses. Nearly all have a personal physician; the percentage of occupancy of the hospital is also similar and in a range indicating that beds are available if needed. The population of different Vermont areas thus appear reasonably well matched on the essential characteristics that predict individual utilization of health care. Also, on an annual basis and for an episode of illness, about the same number of patients in each area contact their physician.

The observation that similar populations living in neighboring areas receive widely differing amounts of care runs counter to an important theory about the market for professional services. This theory holds that lay uncertainty is the critical, distinguishing market factor. In the case of health care, patients are uncertain about the nature of their symptoms or the seriousness of their illnesses; they also do not know the value of a particular treatment nor know the alternatives. Rational behavior in this "information poor" environment requires what in other markets is irrational: delegation of the choice of treatment to the seller, the physician, who recognizes health needs and understands the value of alternative therapies.<sup>13,14</sup>

Yet, quite apart from the data on variations, there is evidence that physicians themselves do not agree on the need or the value of therapies. There are differences among physicians in interpreting or recognizing clinical signs and symptoms and disagreement on the meaning of diagnostic tests.<sup>15,16</sup> Technical innovations in medicine are commonly adopted without controlled tests on outcome and there is considerable skepticism about the claims for effectiveness of many common medical and surgical practices.<sup>17,18</sup>

Awareness of the importance of professional influence on utilization should influence the debate over national health insurance. The popular model for "control" of utilization is directed at the consumer, at the time of contact: to make a patient think twice about the relative importance or seriousness of his illness before consuming care, a deductible or co-payment is assessed. Is this an effective strategy? The Vermont data suggest not. While the homogeneity of insurance resources available to Vermont populations preclude analysis of the effects of varying co-insurance factors, we have seen the co-insurance and deductible provisions of the Medicare Part B program are ineffective in rationalizing strategies for allocation of health care, supporting a nearly three-fold variation in program expenditures.

The major factor in the expenditure differential between Vermont communities is varying use of institutionalized "higher technology" care. Price related factors do not appear to play an important

role in determining the variation in per capita expenditures for hospital care.<sup>9</sup> Within tolerable limits of self-insurance, it is unclear how a patient-directed co-insurance strategy would reduce these variations or lead to better decisions affecting health outcome.

### SUMMARY

The data presented herein make it improbable that consumers determine variations in rates of health care or the per capita expenditure among neighboring areas. Any serious policy directed at the consumption of health care — its increase, decrease, or typology — must directly address the affect on consumption of the providers of health care. The fundamental and unanswered question is the impact on health status of the varying strategies for treating common illnesses.

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# Tuberculous Infection in a State Mental Retardation Facility

TAKANORI KIMURA, M.D., F.A.A.F.P.\* and MARIE E. TWITCHELL, R.N.\*\*

Prevalence of tuberculous infection among the residents at Pineland Center, a State institution for the mentally retarded, has been surveyed for the years 1974 and 1975. Previously, Pineland residents with a negative tuberculin reaction generally received tuberculin skin tests annually; administration and recording methods, however, were not uniform and compilation of institution-wide results was not available, nor are nationwide statistics available on tuberculin reaction rates in residential facilities for the mentally retarded. Our survey utilized the 1974 recommendations of the American Thoracic Society for tuberculin skin test.<sup>1</sup> The results served as a basis for the establishment of a new and more efficient tuberculosis control policy for both residents and employees at Pineland Center.

## MATERIALS AND METHODS

Tuberculin skin tests were performed by intracutaneous injection of 0.1 ml of Purified Protein Derivative (PPD) tuberculin containing 5 tuberculin units into the volar surface of the forearm of each resident. Residents were tested if their past skin test was negative, or not recorded in millimeters, or if their past test was done by multiple puncture test or Patch test. The test was usually read on the third, but in some cases on the second day after injection. The diameter of induration was measured transversely to the long axis of the forearm and recorded in millimeters (mm). Ten (10) mm or more of induration was interpreted as a positive reaction, 5 mm through 9 mm of induration as doubtful, and 0 mm to 4 mm of induration as a negative reaction. A tuberculin converter is defined as a person whose tuberculin reaction has increased by at least 6 mm within 24 months, from less than 10 mm in diameter to 10 mm or more in diameter.<sup>2</sup> The results of tuberculin skin tests for 1974 were compiled from residents' immunization cards.

## RESULTS

Table 1 represents the numbers of tuberculin reactions by age and sex. In 1974, 66 of the 131 positive reactors had been previously tested by multiple puncture or Patch test only, and not confirmed by PPD intracutaneous test. In 1975, the number of those positive reactors who were not confirmed by PPD intracutaneous test was reduced to 5 out of the 128 positive reactors.

TABLE 1

Age Group	Total (%)		Male (%)		Female (%)	
	1974	1975	1974	1975	1974	1975
0-4	—	—	—	—	—	—
5-9	0	0	0	0	0	0
10-14	0	0	0	0	0	0
15-19	2.2	2.2	4.2	2.5	0	0
20-24	21.8	13.3	35.4	22.0	0	0
25-29	33.9	24.6	47.4	32.6	5.6	11.5
30-34	36.4	35.2	48.3	51.5	13.3	9.5
35-39	52.6	34.0	77.3	42.4	18.8	14.3
40-44	71.4	59.4	75.0	87.5	62.5	31.3
45-49	64.7	61.5	50.0	50.0	85.7	75.0
50-54	78.6	72.7	90.0	72.7	33.3	—
55-59	71.4	83.3	100.0	100.0	50.0	75.0
60-64	75.0	83.3	50.0	66.7	100.0	100.0
65-69	83.3	85.7	75.0	66.7	100.0	100.0
70-74	40.0	50.0	66.7	100.0	0	0
75-79	0	—	—	—	0	—
80-84	—	—	—	—	—	—
85+	—	—	—	—	—	—
All Ages*	29.3 (19.0)	25.7 (17.3)	38.1 (22.4)	31.6 (18.1)	14.5 (14.5)	16.2 (16.2)

\*The figures in ( ) are corrected tuberculin positivity rates with the effect of the tuberculosis outbreak in 1965 subtracted.

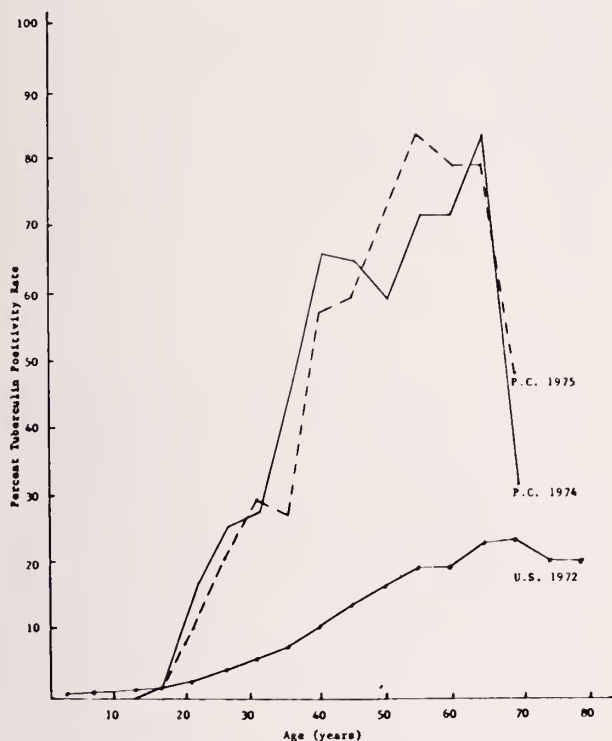
As shown in the table, in 1974, the tuberculin positivity rate for male residents was 38.1 percent (107 of 281 male residents), for female residents 14.5 percent (24 of 166 female residents), and for all Pineland residents 29.3 percent (131 of 447 residents). Corresponding figures for 1975 were 31.6 percent (97 of 307 males), 16.2 percent (31 of 191 females) and 25.7 percent (128 of 498 total residents). When both positive and doubtful reactions were combined, the rates were 41.6 percent for males, 15.7 percent for females and 32.0 percent for all residents in 1974, and 32.9 percent for males, 16.7 percent for females and 26.7 percent for all residents in 1975. There was no tuberculin converter in 1974 or 1975. There was no positive reactor among those residents 14 years of age or younger in either year. The rate of positive reaction generally increased with age, with the highest rate among the 65-69 age group.

The youngest resident tested, both in 1974 and 1975, was 6 years old and the oldest 75 years old. All residents, except two, in each year were white. For purposes of comparison with the rate of tuberculous infection among the general population of the United States, the rates for Pineland Center are corrected for each age group to assume that the Pineland population consists of equal numbers of male and female residents. These rates are shown in

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Fig. 1. Tuberculous Infection by 5-Year Age Groups Pineland Center\* and the United States\*\*.



\*Corrected tuberculin positivity rates at Pineland Center assuming that the Pineland population consisted of equal numbers of male and female residents in each age group.

\*\*Estimated tuberculous infection by 5-year age group, general population of the United States, 1972, furnished by the Center for Disease Control, U. S. Public Health Service.<sup>3</sup>

Figure 1. The corrected positivity rates for all Pineland residents are 26.2 percent in 1974 and 23.9 percent in 1975, as compared with 8.25 percent for the general population of the United States in 1972.

In an attempt to correct the effect of the tuberculosis outbreak at Pineland Center in 1965, which is described below, the 15 cases of the active tuberculosis and the 43 close contacts (who were still residing at Pineland Center in 1974 and 1975), and the number of positive reactors (57 in 1974 and 52 in 1975) among them, were subtracted from corresponding figures. This gives the corrected tuberculin positivity rates for male residents as 22.4 percent in 1974 and 18.1 percent in 1975, and for all Pineland residents as 19.0 percent in 1974 and 17.3 percent in 1975. The positivity rates for female residents remained the same; namely, 14.5 percent in 1974 and 16.2 percent in 1975. Further, if the Pineland population is assumed to have consisted of equal numbers of male and female residents, then the corrected positivity rates for all Pineland residents would be 18.4 percent in 1974 and 17.2 percent in 1975.

## DISCUSSION

Communications with the Center for Disease Control<sup>3</sup> indicate that there are no nationwide

figures available on tuberculin reaction rates in residential facilities for the mentally retarded. Maryland has been the only state to provide specific information on its tuberculin testing program, involving at least four of its five mental hospitals. Their overall rate of positive tuberculin reactors among the patient population was 21.5 percent, 18.2 percent, and 16.8 percent in 1972, 1973, and 1974, respectively. Lack of specific information comparable to that compiled on Pineland residents precludes further analysis.

The resident population at Pineland Center decreased from the maximum of about 1,600 in 1955-59 to about 1,100 in 1965 and to about 500 in 1975. As the resident population decreases, it is the more severely mentally retarded and the multiple-handicapped residents that tend to remain in the institution.

Prior to institution of vigorous tuberculosis control measures at Pineland Center in 1954, up to 48 percent of deaths (12 out of 25 deaths in 1943) were attributed to tuberculosis. Between 1955 and 1960, 83 cases of tuberculosis were under surveillance; 59 of them active tuberculosis. There were no deaths due to tuberculosis in 1955.<sup>4</sup> It appeared that tuberculosis control was successful, but in 1965 an outbreak of tuberculosis occurred in an all-male dormitory at Pineland Center involving 24 male patients with active disease. Eight were reactivation of previously existing lesions and the remaining 16 were new. In 1966, an additional female patient with active tuberculosis was found in an all-female dormitory, and in 1967 another female in a mixed dormitory. Both were reactivations. After the isolation and effective treatment of these active cases, the TB Unit was closed in 1968.<sup>1</sup> The last case of active tuberculosis was found to have radiological evidence of reactivation in 1973 and received retreatment; his medication was discontinued in April, 1975.

The prevalence of tuberculin positive reactors among the United States population is now estimated to be about 7 percent (about 0.2 percent among 6-year-old children and about 0.7 percent among adolescents), as compared with 10-12 percent in 1969, a decline of approximately 75 percent in the last 10 years.<sup>5</sup> The current infection rate is estimated to be 0.02 percent. New active cases of tuberculosis declined by 2.8 percent from 30,998 in 1973 to 30,132 cases in 1974 (15.0 percent decline in Maine from 107 in 1973 to 91 in 1974).<sup>6</sup> The case rates decreased by 4.1 percent from 14.8 to 14.2 per 100,000 population (16.4 percent decrease from 10.4 to 8.7 in Maine). Both white and non-white groups had almost twice as many cases in males as compared with females in 1974. Maine ranked 35th in 1973 and 38th in 1974 for new active tuberculosis case rates. The corrected positivity rates for all Pineland residents, 26.2 percent for 1974 and 23.9 percent for 1975 (18.4 percent for 1974 and 17.2 percent for 1975 if the effect of 1965-tuberculosis

outbreak is subtracted) appears unusually high. The same trend is seen when the rate for each age group is compared with that of the United States population for the corresponding age group in 1972, as furnished by the Center for Disease Control, Tuberculosis Control Division. None of the Pineland residents have received Bacille Calmette Guérin (BCG) vaccination.

False tuberculin test results can arise from four sources: faulty techniques in administering the test, inaccurate measurement of the ensuing reaction, incorrect interpretation of the results, or failure of the tested subject to react in the usual fashion. The American Thoracic Society currently recommends that induration with a diameter of 10 mm or more to 5 TU of PPD be called positive. In populations with a high frequency of tuberculosis infection relative to other mycobacterial infections, the criterion of positivity should be shifted downward. The Maine State Department of Human Services' 1975 recommendations define as positive reactors those with induration with a diameter of 5 mm or more to PPD. Thus, the positivity rates for all Pineland residents are 29.3 percent for 1974 and 25.7 percent for 1975 by the American Thoracic Society Standard, and 32.0 percent for 1974 and 26.7 percent for 1975 by the Maine State Standard. If the effect of 1965-tuberculosis outbreak is subtracted, corresponding figures are 19.0 percent for 1974 and 17.3 percent for 1975 by the American Thoracic Society Standard and 21.9 percent for 1974 and 18.0 percent for 1975 by the Maine State Standard. The American Thoracic Society's recommendations made one exception to their standard: the criterion for a positive tuberculin reaction among suspected cases and close contacts should be reduced from 10 to 5 mm of induration. The declining prevalence of positive reactors among the general population coupled with the fact that there has not been a single converter at Pineland Center in the past few years will undoubtedly further decrease the tuberculin positive rate among the residents at Pineland Center in the future.

In Maine, in 1974, the tuberculin reactor rate among household contacts was 27.8 percent (28.0 percent in the United States), but among non-household contacts it was only 15.3 percent (16.0 percent in the United States). The positive rate of all the contacts examined in the United States was 20.6 percent in 1974.<sup>6</sup> The tuberculin reactor rate among household contacts exposed to active patients with positive smears was 41 percent in Maine in 1972.<sup>7</sup> The positivity rate of 24-26 percent (17-19 percent if the effect of the 1965-tuberculosis outbreak is subtracted) for all Pineland residents in 1974-75 is closer to those figures for household contacts in Maine and the United States than to the national prevalence of positive reactors of 7 percent.

Variables affecting reactions to tuberculin tests must be considered: tuberculin sensitivity does not develop until two to ten weeks after infection has

occurred; approximately 10 percent of children with military or meningeal tuberculosis do not react to tuberculin at the time they come to medical attention; unusual tuberculin reaction can be caused by the so-called booster effect.<sup>8</sup> The use of repeated tuberculin testing to estimate the incidence of new infections (conversion rates) in groups of persons is complicated by the fact that apparent conversions can be caused by the booster effect. Delayed hypersensitivity to tuberculin, once it has been established by infection or vaccination, may gradually wane over the years. On an initial test at this point, these persons may have negative or doubtful reactions. The stimulus of the initial test may then boost or increase the size of the reaction to a second test, sometimes causing an apparent conversion or development of sensitivity. The booster phenomenon is said to be inconsequential among children; it increases with age and is most frequently encountered among persons over 55, but it may occur at any age. The booster effect can be seen on a second test done within a week of the initial stimulating test and can persist for a year, and perhaps longer.

An example can be seen in one of our residents, a 31-year-old male, who was closely exposed to active tuberculosis in 1965. His Patch test was negative in 1964, but a Tine test was positive shortly after exposure in 1965. Isoniazid (INH) prophylaxis was immediately instituted. The next test, PPD (5 TU) intracutaneous, was 6 mm in 1974. Another test was repeated 13 months later, giving a positive reaction of 13 mm of induration. His chest roentgenograms have been consistently negative for any abnormality. This technical conversion by definition can be explained by the booster effect.

Our survey revealed that there was not a single converter, technical or true, except the one mentioned above, at Pineland Center in 1974 or 1975. The definition of tuberculin conversion makes it almost mandatory to have a base-line tuberculin reaction recorded in millimeters. This reading and recording of tuberculin tests has been standardized at Pineland Center since 1975. The nurse epidemiologist has been instrumental in implementing the new policy and compiling the results.

Productivity and cost-benefit effects of tuberculosis control measures have recently been under particularly heavy scrutiny both in the United States<sup>9</sup> and abroad.<sup>10</sup> New guidelines for personnel tuberculosis control program<sup>11</sup> and prevention of tuberculosis transmission in hospitals<sup>12</sup> has been issued. In accordance with the similar recommendations of the Maine State Department of Human Services in September, 1975, combined with our findings that there was not a single true converter among the Pineland residents in 1974 and 1975, Pineland Center has adopted a new policy for tuberculosis control and employee surveillance. This eliminates routine annual chest roentgenograms on residents and employees except those

*Continued on Page 293*

## Tricyclic Antidepressant and Monoamine Oxidase Inhibitor Combination Therapy

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### ABSTRACT

Combinations of monoamine oxidase inhibitors and tricyclic antidepressants are widely considered to be potentially lethal. Many sources suggest that concurrent therapy with these agents is contraindicated and that consecutive therapy requires a wash-out period of from ten to fourteen days. Recently, however, informed opinion has shifted from an absolute contraindication to a cautious recommendation for the combination. The simultaneous administration of these agents is potentially efficacious and safe if carefully monitored and controlled.

The concurrent use of a monoamine oxidase inhibitor (MAOI) and a tricyclic antidepressant (TCA) is considered by many authors to be contraindicated.<sup>1-5</sup> The combination is listed as a "contraindication" in the product literature for imipramine (Presamine<sup>®</sup>, Imavate<sup>®</sup>, SK-Pramine<sup>®</sup>, Tofranil<sup>®</sup>), amitriptyline (Elavil<sup>®</sup>, Endep<sup>®</sup>), protriptyline (Vivactil<sup>®</sup>), nortriptyline (Aventyl<sup>®</sup>), desipramine (Norpramin<sup>®</sup>), tranlycypromine (Parnate<sup>®</sup>), phenelzine (Nardil<sup>®</sup>), isocarboxazid (Marplan<sup>®</sup>), pargyline (Eutonyl<sup>®</sup>), and pargyline-methychlothiazide (Eutron<sup>®</sup>).<sup>6</sup> Doxepin (Sinequan<sup>®</sup>) product information denotes the combination as a "warning" rather than a "contraindication."<sup>6</sup> The contraindication is derived from observations of potential drug toxicity in four areas: (1) the general toxicity occurring with either agent administered singly; (2) the proposed drug-drug interaction; (3) the animal toxicity studies conducted on the combination; and (4) the clinical observations of serious toxicity, sometimes resulting in death.

### GENERAL TOXICITY

The tricyclic antidepressants, administered alone, have a wide range of reported side effects, including psychiatric (delirium and hypomania), neurologic (tremors, headache, extrapyramidal symptoms, seizures), anticholinergic (dry mouth, constipation, blurred vision, mydriasis, cycloplegia, urinary retention, etc.), allergic (jaundice, agranulocytosis), gastrointestinal (nausea, vomiting), and cardiovascular (orthostatic hypotension, cerebrovascular accidents, myocardial infarction, tachycardia, palpitations) manifestations.<sup>1,3,7-9</sup> The cardiac effects are considered to be especially dangerous since they allegedly have caused sudden death in patients both with and without previous heart disease.<sup>10</sup>

The monoamine oxidase inhibitors exhibit a similar array of side effects,<sup>1,3,7-9</sup> plus the potentially fatal interaction with foods containing the pressor substance tyramine.<sup>1,3,10,11</sup> This interaction may occur unexpectedly due to the unpredictable quantities of tyramine in foods.<sup>4,10-12</sup> The tyramine content of foods known to have caused hypertension in patients receiving MAOI therapy are listed in Table 1.<sup>4,12-16</sup> Table 2<sup>4,12-16</sup> lists other foods and amines that have precipitated hypertensive reactions.

Tyramine, 6 mg, can cause a moderate rise in blood pressure,<sup>13</sup> 10 mg may exhibit a marked pressor effect,<sup>1</sup> and 25 mg can produce a severe hypertensive crisis.<sup>13</sup> In Great Britain, phenelzine (Nardil<sup>®</sup>) therapy has been associated with 26 deaths over a 7½ year period, with jaundice being the cause in 15 cases.<sup>17</sup> In addition, three cases of non-fatal intracranial hemorrhage have been documented.<sup>13</sup> Seventeen cases of interactions between phenelzine and foodstuffs were reported between January, 1964, and June, 1973, none of which were fatal.<sup>15</sup> Tranlycypromine (Parnate<sup>®</sup>) therapy has been reported to have caused 21 deaths<sup>4,17</sup> and 14 instances of non-fatal intracranial hemorrhage over a 7½ year period.<sup>13</sup> Of the deaths two were attributed to jaundice, five to "cheese reactions,"<sup>17</sup> three to combination with amphetamines, and three to intracranial hemorrhage due to an unknown precipitant.<sup>13</sup> Eight of the deaths were unexplained. Tranlycypromine's higher incidence of adverse reactions with tyramine-containing foods is most

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TABLE 1

TYRAMINE-CONTAINING FOODS PRECIPITATING HYPERTENSIVE CRISIS <sup>1,12-16</sup>		
Product	Tyramine Content (mcg/gm or ml)	Number of Cases Reported
Cheese	0 — 1,416	67
English cheddar	0 — 953	
Canadian cheddar	231 — 535	
New York State cheddar	1,416	
New Zealand cheddar	417 — 500	
Kraft, cheshire	ND <sup>a</sup>	
Camembert	86	
Stilton	466	
Brie	180	
Emmenthaler	225	
Gruyere	516	
cottage cheese	NS <sup>b</sup>	
cream cheese	NS	
processed American	ND	
Yeast products	0 — 1.6	3
yeast	ND	
yogurt	NS	
"Marmite"	1.6	
Alcohol	0 — 25.4	5
beer	1.8 — 4.4	
wines	0 — 25.4	
sherry	3.6	
sauterne	0.4	
reisling	0.6	
chianti	25.4	
port	ND	
Pickled herring	0 — 3,030	2
Fermented sausage (summer, etc.)	S <sup>c</sup>	—
Liver	50 — 274	
fresh chicken	ND	
aged chicken	94 — 113	
fresh beef	50 — 65	
aged beef	274	
Cream	0 — S	3
Bananas	0 — 65	—
skin	65	
fresh pulp	NS	
rotten pulp	S	
Avocados	NS — S	—
Canned figs	MS — S	—

<sup>a</sup>ND = tyramine levels were not detectable

<sup>b</sup>NS = tyramine levels were not significant

<sup>c</sup>S = tyramine levels were significant but no specific value was given

likely due to its efficacy in inhibiting intestinal MAO.<sup>13</sup>

Bickel<sup>18</sup> reviewed 106 cases of intoxication with tricyclic antidepressants resulting in severe or fatal reactions. In adults, imipramine proved fatal in doses ranging from 10 to 88 mg/kg and amitriptyline proved fatal in doses ranging from 15 to 69 mg/kg.<sup>18</sup>

Gander<sup>19</sup> found that in more than 80% of patients treated with a combination of an MAOI and TCA, side effects were either absent or inconsequentially mild. In ten percent of the patients on combination therapy and seven percent of those receiving one drug alone, side effects warranted a modification of dosage or discontinuation of therapy.

#### DRUG INTERACTION

Three mechanisms of interaction have been pro-

TABLE 2

#### OTHER AMINES WHICH PRECIPITATE HYPERTENSIVE CRISIS<sup>4,12-16</sup>

Product	Amine	Number of Cases Reported
Chocolate	vanillin	1
Broad beans	dopa	2
Bananas	serotonin	—

posed in the literature:<sup>20</sup>

1. MAOI inhibit the enzymes responsible for the metabolic inactivation of TCA.
2. MAOI act on liver enzymes to alter TCA catabolism such that abnormal but active TCA metabolites are produced.
3. The interaction causes an intensification of the action of amines present in the central nervous system by stimulating further release or by augmenting the pharmacologic activity of existing amines.

The third mechanism appears most valid because, unlike the first, it accounts for the difference between the toxic reactions encountered in a single-entity and combination drug overdose cases. For example, death from an overdose of imipramine stems from respiratory depression with only a mild hyperpyrexia (approximately 1°C), whereas death after administration of the combination of an MAOI and imipramine stems from hyperpyrexia in rabbits.<sup>20</sup> Intraventricular administration of 5-hydroxytryptamine resulted in a fall or no change in the rectal temperature in rabbits, but intraventricular administration of norepinephrine (levarterenol or noradrenaline) resulted in a rise or no change in the rectal temperature.<sup>20</sup> Imipramine<sup>4,20,21</sup> and amitriptyline<sup>21</sup> predominantly influence the reuptake of norepinephrine. Clomipramine<sup>21</sup> has a greater effect of the reuptake of 5-hydroxytryptamine. The hyperpyrexia response observed from the combination of an MAOI and a TCA are due to the increased brain amine levels caused by the MAOI and the more selective inhibition of the reuptake of norepinephrine resulting in enhanced levels of norepinephrine in the brain.<sup>4,20</sup> This third mechanism also explains the increased cardiovascular toxicity of the combination due to the augmentation of the pressor effect of norepinephrine.<sup>22</sup>

#### ANIMAL STUDIES

Studies on albino rabbits by Loveless and Maxwell<sup>20</sup> are representative of other animal investigations of the MAOI-TCA combination. A MAOI (tranylcypromine, phenelzine, or nialamide) was given intraperitoneally 42 and 18 hours prior to intravenous infusion of a TCA (imipramine, amitriptyline, or trimipramine). The doses of all drugs were close to or exceeded the dosages usually associated with 50 percent mortality (LD<sub>50</sub>) in this species. Imipramine consistently produced fatal hyperpyrexia. With a 5 mg/kg dose of this drug, 7 of 13 animals died with 100 mg of concurrent tranylcypromine, 5 of 6 died with concurrent phenelzine (50

mg), and 6 of 6 died with concurrent nialamide (100 mg). Amitriptyline appeared to be less toxic. One fatality occurred with tranlycypromine (100 mg) together with amitriptyline (10 mg). A 5 mg dose of amitriptyline proved to be fatal in 11 of 14 animals when given with 50 mg of phenelzine; with nialamide (100 mg), amitriptyline, 5 mg, was fatal in 5 of 6 animals.

Animal studies such as this were the major documentation for the severe restrictions on combination therapy. The consistent lethality of imipramine was considered conclusive, even though amitriptyline appeared substantially less toxic and no fatalities occurred with trimipramine. Furthermore, the investigators noted that the MAOI doses utilized were greater than those needed for MAOI inhibition *in vivo* and were in themselves potentially toxic. The TCA doses also were very high.

### CLINICAL OBSERVATIONS

#### *Fatal Overdose Due to Single Drugs*

The most convincing evidence against antidepressant drug combinations is the serious and sometimes fatal toxicity often reported following overdosage of either taken alone. In 1968, the National Poisons Information Service in Great Britain reported that the antidepressant drugs, especially amitriptyline, nortriptyline, protriptyline and imipramine, alone and often with other products, were significant contributors to intentional and accidental poisonings.<sup>23</sup> In Great Britain, the number of successful suicides due to TCA overdose increased from 127 to 167 between 1973 and 1974. These figures represent 7.3 and 9.0 percent, respectively, of the total suicidal poisonings in England.<sup>24,25</sup>

#### *Fatal Overdoses Involving Combination Therapy*

Sargent,<sup>26</sup> Schuckit,<sup>27</sup> and Sethna<sup>28</sup> have reviewed the literature describing cases of toxicity attributed to combined therapy. In all such cases the morbid and fatal events were due to an overdose, a "cheese reaction," another medical problem, or the sequential use of TCA shortly after an MAOI. Except in the overdose cases or where another medical problem intervened, all the patients recovered.<sup>27</sup>

Davies,<sup>29</sup> in 1960, reported a 23-year-old female who was ingesting high doses (40 tablets per day) of phenmetrazine (Preludin®). She was "withdrawn" using chlorpromazine over a three-week period. Phenelzine, 45 mg per day, was substituted for another 21 days, then imipramine, 75 mg per day, was added. She took 200 to 300 mg imipramine instead of the prescribed dose and subsequently died four hours after hospital admission. Clinical findings included profuse diaphoresis, extreme restlessness and hyperexcitability, collapse, and death secondary to hyperpyrexia (109°F).

Babiak,<sup>30</sup> in 1961, reported a 26-year-old male who ingested 600 mg of imipramine and 13 Parstelin (130 mg of tranlycypromine and 13 mg of trifluoperazine). His temperature rose to 107.8°F,

and his blood pressure, which was 180/60 mmHg on admission, fell to 70 mmHg systolic. Death occurred approximately six hours after admission.

Bowen,<sup>31</sup> in 1964, reported a 41-year-old female who was hospitalized with tachycardia (150 beats per minute) and fever (104°F). The cause of death was diagnosed as heart failure secondary to myocardial degeneration precipitated by the combined action of antidepressant drugs. Controversy surrounds this report. The woman's husband claimed that she was faithfully taking phenelzine, 45 mg per day. Although desipramine had been prescribed six weeks earlier, she was not taking the drug on a regular basis, and it was alleged that the patient had not taken desipramine within 48 hours of her death. On the morning of her death, she had taken chlorpromazine, although she usually only took this as a sedative at bedtime. The pathologist found "therapeutic" levels of chlorpromazine and desipramine in tissues but no phenelzine. Although no phenelzine could be found, it was suggested by the pathologist that this could still have produced the serious reaction even if it had not been taken for a number of days. The pathologist concluded that death was caused by a combination of the MAOI and TCA. Sargent<sup>32</sup> replied to the Bowen case report, indicating that the woman had been successfully treated with phenelzine, 45 mg per day, and amitriptyline, 150 mg per day, on two separate occasions without side effects. He also questioned the pathologist's conclusion since phenelzine was not found in the body. The only evidence that a desipramine overdose had not occurred was the number of tablets remaining in the bottle. Hall,<sup>33</sup> the pathologist for the case, replied to the criticism and restated his position that no overdose existed.

Stanley,<sup>34</sup> in 1964, described a 22-year-old male alcoholic, apparently abstinent, who was prescribed phenelzine, 45 mg per day. Because he began drinking again, imipramine was substituted. However, the imipramine therapy made him excessively drowsy and phenelzine was restarted. He was instructed not to start the phenelzine until he had discontinued the imipramine for a total of 4 days. Instead, he ingested between 450 and 600 mg of phenelzine, approximately 20 imipramine tablets of an unknown strength, and resumed drinking heavily. He died one hour after hospital admission. Clinical findings included a heart rate of 150 beats per minute, blood pressure of 160/100 mmHg, temperature of 110°F, and potentially toxic blood levels of phenelzine and imipramine.

Saunders,<sup>35</sup> in 1965, reported a 37-year-old male who had taken etryptamine (Monase®), 45 mg per day, for 10 days. It was discontinued and replaced with amitriptyline, 75 mg per day, for the next five days. Because he experienced visual hallucinations, the patient was admitted to the hospital and initially treated with promazine, phenobarbital, and paraldehyde. The patient apparently was a heavy drinker and had experienced episodes of transient jaundice

four years earlier and two weeks prior to admission. Between 24 and 60 hours after admission the patient experienced hyperexcitability, fluctuations in blood pressure and body temperature, congestive heart failure, and anuria. The patient expired approximately 60 hours after admission. Autopsy revealed damage of the liver and kidneys.

Sargent<sup>24,36</sup> reported two patients on combination therapy who died with findings suggestive of drug toxicity. However, an autopsy on the first patient,<sup>37</sup> revealed a volvulus of the small intestine which proved to be the cause of death. The second patient, who had three months of therapy with tranylcypromine-trifluoperazine combination (Parstelin) together with trimipramine died suddenly. At autopsy, a large volume of macaroni and cheese, ingested an hour before hospital admission, was found in the stomach.

In each of these cases, with the exception of the controversial Bowen case, an overdose was taken, a complicating medical problem intervened, or a tyramine-induced hypertensive crisis was the precipitating factor. The Saunders<sup>35</sup> case emphasizes the interaction of all the physiological factors. Since both hydrazine-MAOI and TCA may produce jaundice as a non-dose related side effect,<sup>1,3,7</sup> a patient with a history of jaundice and/or heavy drinking is probably predisposed to this toxicity. A final consideration in the Saunders<sup>35</sup> case and the Bowen<sup>31</sup> case, is the possible interactions of alcohol, barbiturates and phenothiazines with MAOI and TCA. Numerous anecdotal reports have suggested possible adverse interactions among these agents.<sup>1,37,38</sup> The combination of amitriptyline and alcohol has apparently resulted in two deaths.<sup>39</sup>

#### *Near-Fatalities Involving Combination Therapy*

Near-fatal reactions have involved three types of situations: (1) attempted suicide with overdoses of antidepressants, other drugs and/or foods containing high tyramine levels; (2) adverse reactions associated with multiple drug abusers; and (3) adverse reactions occurring with therapeutic doses.

*Deliberate self-poisoning.* Luby, et al<sup>40</sup> reported a 30-year-old female, who, after suicide attempts with aspirin, was treated with tranylcypromine, 75 mg per day. Following a fight with her husband, resulting in a return of her depression, imipramine, 100 mg per day, was substituted for tranylcypromine. Within one week she made a third suicide attempt by ingesting 175 mg tranylcypromine and 275 mg of imipramine. Vital signs were: blood pressure 120/60 mmHg, heart rate 124 beats per minute, respiratory rate 32 per minute, and temperature 105.6°F. Within 24 hours, she regained consciousness but memory loss and confusion persisted for two weeks.

Jarecki<sup>41</sup> reported a 38-year-old female who attempted suicide with phenelzine 180 mg, amitriptyline 800 gm, an unknown but small amount of aspirin, and chlorpheniramine. She had been taking amitriptyline 150 mg per day for 12 weeks. Her vital

signs were variable with blood pressure ranging from 150/80 to 90/60 mmHg, heart rate 90 to 100 beats per minute, and temperature ranging from normal to 100°F. She was alert by the third day after hospital admission.

Simmons<sup>42</sup> reported a 19-year-old male who ingested 25 Parstelin (250 mg of tranylcypromine and 25 mg of trifluoperazine) tablets, 100 mg of protriptyline, and two cheese rolls. Upon admission, vital signs were: temperature 101°F, heart rate 130 beats per minute, and blood pressure 190/90 to 260/0 mmHg. He was comatose for 48 hours. Twenty-four hours after regaining consciousness, all signs were normal.

In each of these cases, the reaction was attributed to the improper usage of the antidepressant drugs.

*Multiple drug use.* Adverse reactions have also occurred in multiple drug users. Chappell<sup>43</sup> reported a 43-year-old female who developed hypothermia and hypotension seven days after the substitution of amitriptyline, 100 mg per day, for isocarboxazid (Marplan®), 30 mg per day, with three days of "washout" in between. She was also taking sodium amobarbital, perphenazine and unspecified amounts of wine and other alcoholic beverages.

Hypertension, hyperpyrexia and convulsions were reported by Man<sup>44</sup> in a 43-year-old female taking 15 different drugs simultaneously, including chlorpromazine, trihexiphenidyl, phenobarbital, phenelzine, and amitriptyline. Her toxic manifestations were attributed to the "MAOI and other psychotropic drugs."<sup>44</sup> This conclusion has been disputed in the literature.<sup>45</sup>

Delirium tremens was mistaken for an adverse reaction of combined therapy with tranylcypromine and trimipramine.<sup>36</sup> The patient experienced hallucinations, twitching of the limbs, fever, tachycardia, and profuse sweating. The physician and the patient's mother were insistent that no other drugs had been taken in excess, and the only drugs used were those prescribed. It was later determined that he had been taking high doses of carbromal with pentobarbital and was in his fourth day of sedative withdrawal.<sup>36</sup>

*Therapeutic doses.* Non-fatal adverse reactions have occurred when therapeutic doses of MAOI were given first and then followed by a TCA administered parenterally. In all three reported cases,<sup>39,46,47</sup> the MAOI was phenelzine and the tricyclic was imipramine. The reaction occurred within 16 hours after the initial dose.

Toxic, non-fatal reactions manifested by agitation, tremulousness, restlessness, delirium, generalized clonic convulsions, hyperthermia, and increased pulse, respiration and blood pressure have also followed oral administration of a MAOI and TCA. McCurdy and Kane<sup>48</sup> reported a woman receiving pargyline who took one 25 mg imipramine tablet from a prior prescription. Ayd<sup>49</sup> reports of two instances of toxicity. The first involved the use of iproniazid, 75 mg per day, with a later addition of

TABLE 3

## STUDIES OF COMBINED MAOI AND TRICYCLIC ANTIDEPRESSANT THERAPY

Study	Number of Patients	Tricyclic Drug	Dosage (mg/day)	MAOI	Dosage (mg/day)	Number Discontinued Due to Side Effects
Schuckit <sup>26</sup>	36	Imipramine	50 — 100	Isocarboxazid	10 — 40	0/50
	6	Amitriptyline	50 — 100	Isocarboxazid	23 — 30	
	3	Amitriptyline	75	Tranlycypromine	30	
	2	Nortriptyline	75	Isocarboxazid	30	
	1	Desipramine	100	Tranlycypromine	30	
	2	Protriptyline	20	Tranlycypromine	20	
Winston <sup>60</sup>	13	Amitriptyline	25 — 100	Isocarboxazid	5 — 30	4/20
	6	Amitriptyline	10 — 100	Tranlycypromine	10 — 30	
	1	Imipramine	10 — 100	Tranlycypromine	10 — 30	
Sethna <sup>27</sup>	12	Amitriptyline	75	Phenelzine	45	2/12
Ayd <sup>49</sup>	55	Doxepin	150 — 200	Tranlycypromine	50	8/157
Gander <sup>7</sup>	98	Amitriptyline	150 max.	Phenelzine	45 max.	
	22	Amitriptyline	150 max.	Isocarboxazid	45 max.	
	19	Amitriptyline	150 max.	Iproniazid	45 max.	
	9	Imipramine	150 max.	Phenelzine	45 max.	
	5	Imipramine	150 max.	Isocarboxazid	45 max.	
	7	Imipramine	150 max.	Iproniazid	45 max.	
	11	Other combination				
Spiker <sup>61</sup>	8	Amitriptyline	150 max.	Isocarboxazid		12/201
	41	Amitriptyline	150 max.	Phenelzine	45	
	28	Amitriptyline	150 max.	Tranlycypromine		
	77	Imipramine	150 max.	Isocarboxazid		
	14	Imipramine	150 max.	Phenelzine	45	
	14	Imipramine	150 max.	Tranlycypromine		
	2	Other		Isocarboxazid		
	5	Other		Phenelzine		
Sargent <sup>62</sup>	7	Other		Tranlycypromine		0/66
	51	Amitriptyline	75 — 150	Isocarboxazid	30	
	51	Amitriptyline	75 — 150	Iproniazid	75 — 150	
	5	Imipramine	150	Iproniazid	75 — 150	
	5	Amitriptyline + imipramine		Phenelzine	45	

imipramine, 75 mg per day. Toxic reactions occurred after the third dose of imipramine. The second case involved the use of isocarboxazid by a patient for three months. After discontinuing the isocarboxazid, imipramine was started without interruption of therapy. Toxicity developed after six doses of imipramine. Howarth<sup>50</sup> reported a 76-year-old female, who after three weeks of phenelzine therapy, was given a 50-mg dose of imipramine with 15 mg of phenelzine simultaneously due to an error. A toxic reaction ensued. Brachfeld, et al<sup>51</sup> suggested that three weeks of tranlycypromine discontinued for three days can still precipitate a toxic response after "one tablet" of imipramine.

Two instances of toxicity have been reported involving the use of a tricyclic followed by a MAOI. The first report<sup>52</sup> involved a female taking imipramine for several weeks; after one 15-mg tablet of etryptamine (Monase<sup>®</sup>) she developed a toxic reaction. The other report<sup>53</sup> involved the use of imipramine for 19 days which was discontinued and immediately followed by tranlycypromine. Six days after discontinuation of the imipramine, toxic reactions occurred.

Non-fatal toxic reactions have developed under all sets of circumstances and with all combinations of agents. The time interval between dosage and onset of toxicity appears to be important. When a tricyclic is added to an MAOI regimen, toxicity

appears to develop within at least three doses, whereas when a MAOI is added to a tricyclic regimen, the toxicity appears to be delayed up to 6 days.

## EFFICACY OF COMBINATION THERAPY

In numerous studies involving nearly 600 patients with refractory depression or phobic anxiety states, the combinations of MAOI's and TCA's have proved to be both safe and effective<sup>7,19,21,27,28,54-61</sup> (see Table 3). The incidence of side effects is approximately the same as with single drug therapy.<sup>7,19,27,38</sup> The most significant side effect reported from the combination is excessive weight gain due to an increase in appetite and serum insulin levels.<sup>62</sup>

The Food and Drug Administration has granted investigational status for further study of this combination.<sup>63</sup> The American Pharmaceutical Association in its *Evaluations of Drug Interactions* (second edition)<sup>64</sup> has reclassified the combination. It is no longer contraindicated, and recommendations for safe usage are given. Hansten<sup>37</sup> views the combination as safe if the following precautions are observed:

1. Avoid large doses
2. Give the drugs orally
3. Avoid tranlycypromine
4. Avoid imipramine and clomipramine
5. Monitor the patient closely

## USAGE CONDITIONS

The following considerations appear pertinent to the use of MAOI-TCA combinations.

### Patient Selection<sup>64</sup>

Only refractory patients in whom less hazardous treatment measures have failed should be considered for combination therapy. Safer treatment measures consist of an adequate trial (at least four weeks) of a MAOI or a TCA individually at therapeutic doses. At least 14 days of "washout" should elapse when changing from a MAOI to a TCA, and at least 10 days between a TCA and a MAOI. Patients should be evaluated medically to insure good general physical health, particularly normal hepatic and cardiac function. Only those patients who are responsible enough to take their medication exactly as prescribed and who will adhere to dietary restrictions should be considered. Alcoholics, drug "abusers," and individuals taking multiple medications should be excluded.

### Dosage Schedule

Although all of the currently marketed drugs have been combined safely, some drugs appear better candidates for combination. Amitriptyline is recommended over imipramine<sup>21,60,65</sup> because it is sedative whereas imipramine is stimulating.<sup>21,66</sup> Amitriptyline is less likely than imipramine to sensitize the patient to norepinephrine because its norepinephrine reuptake inhibition is countered by a blocking effect on the norepinephrine receptor sites.<sup>21</sup> The use of hydrazine MAOI rather than a nonhydrazine agent also is indicated. Tranlycypromine use is considered more hazardous<sup>65</sup> because of the higher incidence of hypertensive crises and tyramine reactions associated with its use. Isocarboxazid has been suggested as potentially safer because it is a "pure MAOI" as compared to tranlycypromine and phenelzine, which exhibit "amine releasing" properties in addition to their MAOI inhibition, thus predisposing the patient to hypertensive attacks.<sup>65</sup> Phenelzine has also caused problems due to genetic variability in rates of clearance by acetylation. The response to phenelzine therapy is better in slow acetylators than in fast<sup>67,68</sup> due to higher drug levels in the slow acetylators. However, the incidence of side effects also is higher.<sup>67</sup> In one study it was found that most patients with severe side effects were slow acetylators.<sup>68</sup>

The preferred dosage regimen constitutes administration of the MAOI during the day, usually on a "t.i.d." regimen, while the entire dose of the TCA is administered at bedtime to take advantage of sedative effects.<sup>26,56,60</sup>

The route of administration should be oral.<sup>37</sup> The safest approach to initiate therapy is to stop all drugs, wait an appropriate length of time, such as 10 to 14 days,<sup>3,4</sup> then begin the drugs together.<sup>65</sup> A beginning dosage of 25 to 50 mg per day of the TCA and 15 mg per day of the MAOI can be slowly

increased over the next two to three weeks to maximum doses of 150 and 45 mg per day, respectively. The dosages used are generally slightly lower than the recommended individual therapeutic dose.

### Patient Education

Patients should be informed of potential side effects and the immediate need for medical advice should side effects occur. Klein<sup>69</sup> recommends having the patient carry 300 mg of chlorpromazine at all times, with the directions to take it orally if a "sudden, throbbing, radiating, occipital headache" occurs, and to seek medical help immediately. Clinicians should also consider obtaining written informed consent from the patient. In cases of severe hypertensive crisis, alpha adrenergic blocking agents, i.e., phentolamine, are the drugs of choice.<sup>64</sup>

## CONCLUSION

Refractory depression is a debilitating disease. An alternative to the present methods of treatment can be the combination of a MAOI and a TCA. Carefully monitored combination therapy in appropriately selected patients is potentially beneficial and has an acceptably low potential for serious toxicity.

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## OBSOLETE PROCEDURES BEING CUT

The National Blue Shield Association is encouraging state Blue Shield Plans to end routine payment for 28 medical procedures which have been judged unnecessary under certain circumstances.

The new cost control effort, called the Medical Necessity Program, was recently announced by William E. Ryan, President of the Blue Shield Association. The program was developed with the aid of the American College of Physicians, the American College of Radiology and the American College of Surgeons.

"If there is a clear need for any of the procedures, Blue Shield will pay for them," Ryan said. "The point of this program is to encourage medical professionals to think about the costs of the procedures they order."

The 28 procedures were identified because each fits into one of four specific categories: 1) new procedures of unproven value; 2) established procedures of questionable current usefulness; 3) procedures which tend to be redundant when performed in combination with other procedures; and 4) diagnostic procedures which are unlikely to provide a physician with additional information when they are repeated again and again.

Surgical procedures listed include: 1) ligation of internal mammary arteries, unilateral or bilateral; 2) radical hemorrhoidectomy, Whitehead type; 3) omentopexy (portal obstruction); 4) kidney decapsulation, unilateral and bilateral; 5) perirenal insufflation; 6) nephropexy; 7) circumcision, female; 8) hysterotomy; 9) supracervical hysterectomy; 10) uterine suspension; 11) uterine suspension with presacral sympathectomy; 12) hypogastric or presacral neurectomy; 13) fascia lata by stripper; 14) fascia lata by incision; 15) ligation of femoral vein, unilateral and bilateral; 16) excision of carotid body tumor; 17) sympathectomy, thoracolumbar, unilateral or bilateral; and 18) sympathectomy, lumbar.

Diagnostic procedures named include: 1) basal metabolic rate (BMR); 2) protein bound iodine (PBI); 3) icterus index; 4) ballistocardiogram (BCG); 5) phonocardiogram with interpretation and report; 6) angiocardiology using carbon dioxide, supervision and interpretation only; 7) angiocardiology, single plane, supervision and interpretation only and in conjunction with cineradiography; 8) angiocardiology, multiplane supervision and interpretation only in conjunction with cineradiography; 9) angiography-coronary, unilateral, selective injection, supervision and interpretation only, single view unless in an emergency; and 10) angiography extremity.

The Medical Necessity Program is still under study in Maine. At present it looks as though some of the 28 surgical and diagnostic procedures listed by the Blue Shield Association are no longer widely used here and could constitute a base for a Medical Necessity Program in Maine. You will be kept up to date as the Maine study progresses.

# Maine Medical Association

## STANDING COMMITTEES — 1977-1978

Standing Committees for 1977-1978 as proposed by the Committee on Nominations and approved at the Second Meeting of the House of Delegates of the Maine Medical Association at Rockport, Maine, June 12, 1977.

### Council on Health Manpower and Education

#### Committee on Allied Health Professions

- A. Dewey Richards, M.D., 180 Main St., Orono 04473 (2 yrs.) — Chairman  
Robert G. MacBride, M.D., 25 Washington St., Lubec 04652 (1 yr.)  
Buell A. Miller, M.D., 260 Western Ave., So. Portland 04106 (1 yr.)  
Elihu York, M.D., 62 Baribeau Dr., Brunswick 04011 (1 yr.)  
Russell A. Morissette, M.D., 185 Webster St., Lewiston 04240 (2 yrs.)  
Doris S. Pennoyer, M.D., 112 Vaughan St., Portland 04102 (2 yrs.)

#### Committee on Continuing Education

- Henry J. Wheelwright, M.D., Augusta Gen. Hosp., Augusta 04330 (2 yrs.) — Chairman  
James A. Edmond, M.D., 191 Lincoln Ave., Rumford 04276 (1 yr.)  
Alfred Hurwitz, M.D., 10 Abenaki Rd., Augusta 04330 (1 yr.)  
Michael C. Bach, M.D., 97 Campus Ave., Lewiston 04240 (1 yr.)  
Floyd B. Goffin, M.D., Pennellville Rd., Brunswick 04011 (2 yrs.)  
Alroy A. Chow, M.D., Box 1245, Presque Isle 04769 (2 yrs.)  
Robert H. Brown, M.D., MRC, Box 45, Bangor 04401 (3 yrs.)  
Albert Aranson, M.D., Maine Med. Ctr., Portland 04102 (3 yrs.)  
Joe R. Wise, Jr., M.D., 263 State St., Bangor 04401 (3 yrs.)

- David R. Ginder, M.D., 325A Kennedy Mem. Dr., Waterville 04901 (3 yrs.)  
Robert L. Ohler, M.D., Box 58, Winthrop 04364 (3 yrs.)  
George E. Sullivan, M.D., 100 College Ave., Waterville 04901 (3 yrs.)

#### Committee on Recruitment, Aid & Placement

- Ferris S. Ray, M.D., 7 Bramhall St., Portland 04102 (3 yrs.) — Chairman  
Robert E. McAfee, M.D., 7 Bramhall St., Portland 04102 (1 yr.)  
Donald M. Robertson, M.D., Box 188, Milbridge 04658 (1 yr.)  
Charles H. Lightbody, M.D., No. Main St., Guilford 04443 (2 yrs.)  
A. Dewey Richards, M.D., 180 Main St., Orono 04473 (2 yrs.)  
Margaret H. Hannigan, M.D., 10 High St., Lewiston 04240 (3 yrs.)

#### Committee on Scientific Programs

- Harold N. Burnham, M.D., 130 Main St., Gorham 04038 (1 yr.) — Chairman  
George E. Davis, Jr., M.D., 12 Spruce St., Augusta 04330 (2 yrs.)  
Don L. Maunz, M.D., 186 State St., Bangor 04401 (2 yrs.)  
David G. Reed, M.D., Rt. #3, Skowhegan St., Camden 04843 (3 yrs.)  
Dana M. Whitten, M.D., Medical Building, Northport Ave., Belfast 04915 (3 yrs.)

### Council on Medical Services

#### Committee on Care of the Disadvantaged

- John J. Pearson, M.D., 271 Center St., Old Town 04468 (1 yr.)  
Joseph B. Alley, M.D., 59 W. Main St., Dover-Foxcroft 04426 (1 yr.)  
David C. Dixon, M.D., Box 792, Farmington 04938 (2 yrs.)  
Dorothy I. Eisengart, M.D., 175 Silver St., Waterville 04901 (2 yrs.)  
Stephen A. Sokol, M.D., 10 High St., Lewiston 04240 (2 yrs.)  
Ruth E. Endicott, M.D., Grasshopper Lane, Ogunquit 03907 (3 yrs.)

#### Committee on Emergency Medical Service

- John W. Towne, M.D., 325C Kennedy Mem. Dr., Waterville 04901 (1 yr.) — Chairman  
John F. Egan, M.D., RFD #3, Box 37A, Turner Road, Auburn 04210 (1 yr.)  
Frank H. Lawrence, M.D., 22 Bramhall St., Portland 04102 (1 yr.)  
John C. Menges, M.D., Central Me. Med. Ctr., Lewiston 04240 (1 yr.)  
Winford C. Adams, M.D., 14 Starlight Dr., Brewer 04412 (2 yrs.)  
Henry B. Finks, M.D., 22 Lunt Rd., Falmouth 04105 (2 yrs.)  
Eric F. Nicholas, M.D., Mars Hill 04758 (2 yrs.)  
Euclid M. Hanbury, Jr., M.D., Medical Bldg., Belfast 04915 (3 yrs.)  
Gordon T. Paine, Jr., M.D., Penob. Bay Phy. Bldg., Glen Cove, Rockland 04841 (3 yrs.)

#### Committee on Government Health Activities

- Raymond E. Culver, M.D., 325 Kennedy Mem. Dr., Waterville 04901 (3 yrs.) — Chairman  
Samson Fisher, M.D., 26 College Ave., Waterville 04901 (1 yr.)  
John H. Steeves, M.D., Rt. #3, Skowhegan 04976 (2 yrs.)  
Richard B. Stephenson, M.D., 169 State St., Portland 04101 (2 yrs.)  
Frederick C. Holler, M.D., 10 High St., Lewiston 04240 (3 yrs.)

#### Committee on Health Care Financing

- Charles H. Lightbody, M.D., No. Main St., Guilford 04443 (2 yrs.) — (Piscataquis) — Chairman  
Harold E. Knuuti, M.D., Medical Bldg., Belfast 04915 (2 yrs.) — (Waldo)  
Ferris S. Ray, M.D., 7 Bramhall St., Portland 04102 (2 yrs.) — (Cumberland)  
Louis Bachrach, M.D., 85 Baribeau Dr., Brunswick 04011 (2 yrs.) — (Linc.-Sag.)  
(3 yrs.) — (Franklin)  
Jerome Dunst, M.D., Rumford Com. Hosp., Rumford 04276 (3 yrs.) — (Oxford)  
H. Clement Jurgeleit, M.D., 316 State St., Bangor 04401 (3 yrs.) — (Penobscot)  
John Kazutow, M.D., Box 113, Columbia Falls 04623 (3 yrs.) — (Washington)  
Harland G. Turner, M.D., Box 38, Norridgewock 04957 (3 yrs.) — (Somerset)

Joseph R. Crawford, M.D., 12 Spruce St., Augusta 04330 (1 yr.) — (Kennebec)  
 Charles W. Steele, M.D., 472 Main St., Lewiston 04240 (1 yr.) — (Androscoggin)  
 John B. Madigan, M.D., Houlton 04730 (1 yr.) — (Aroostook) (1 yr.) — (Hancock)  
 Peter R. Shrier, M.D., 87 Limerock St., Rockland 04841 (1 yr.) — (Knox)  
 Conner M. Moore, M.D., Pine Ridge Road, Saco 04072 (1 yr.) — (York)

#### **Members of the Advisory Committee to the Committee on Health Care Financing**

Maine Society of Anesthesiology — George W. Bostwick, M.D., P.O. Box 388, Newcastle 04553  
 Maine Chapter, American Academy of Family Physicians — A. Dewey Richards, M.D., 180 Main St., Orono 04473  
 Maine Society of Obstetrics and Gynecology — Buell A. Miller, M.D., 260 Western Ave., So. Portland 04106  
 Maine Chapter, American Academy of Pediatrics — Charles E. Burden, M.D., 1 North St., Bath 04530  
 Maine Society of Internal Medicine (Includes Medical Specialty Group) — Harry A. Bliss, M.D., 128 Chadwick St., Portland 04101  
 Section on Ophthalmology of the MMA — Kevin Hill, M.D., 325A Kennedy Mem. Dr., Waterville 04901  
 Maine Radiological Society — John F. Gibbons, M.D., 22 Bramhall St., Portland 04102  
 Maine Chapter, American College of Surgeons — John F. Reynolds, M.D., 325 Kennedy Mem. Dr., Waterville 04901  
 Ear, Nose and Throat Group — Loring W. Pratt, M.D., 325 Kennedy Mem. Dr., Waterville 04901  
 Maine Neurosurgical Society — Daniel A. Rock, M.D., 477 Main St., Lewiston 04240  
 Maine Trauma Committee — H. Carl Amrein, M.D., 29 Weston Ave., Madison 04950  
 Maine Psychiatric Association — Aldo F. Llorente, M.D., 56 Baribeau Dr., Brunswick 04011

Maine Academy of Orthopedic Surgeons — Allan J. Stinchfield, M.D., 16 E. Chestnut St., Augusta 04330  
 Maine Neurological Society — Karl E. Sanzenbacher, M.D., 325C Kennedy Mem. Dr., Waterville 04901  
 Maine Society of Allergy and Clinical Immunology — Thomas F. Conneen, M.D., 131 Chadwick St., Portland 04102

#### **Committee on Hospital Association Liaison**

Euclid M. Hanbury, Jr., M.D., Medical Bldg., Belfast 04915 (3 yrs.) — Chairman  
 John F. Gibbons, M.D., 22 Bramhall St., Portland 04102 (1 yr.)  
 Paul J. Killoran, M.D., Knox Co. Gen. Hosp., Rockland 04841 (2 yrs.)  
 Richard C. Leck, M.D., Bath Mem. Hosp., Bath 04530 (3 yrs.)

#### **Committee on Peer Review**

George W. Wood, III, M.D., 840 Broadway, Bangor 04401 (3 yrs.) — Chairman  
 Arthur K. Carton, M.D., 7 Park St., Houlton 04730 (1 yr.)  
 Earle M. Davis, M.D., 325 Kennedy Mem. Dr., Waterville 04901 (1 yr.)  
 Brian M. Dorsk, M.D., 180 Park Ave., Portland 04102 (1 yr.)  
 John Kazutow, M.D., Box 113, Columbia Falls 04623 (1 yr.)  
 Buell A. Miller, M.D., 260 Western Ave., So. Portland 04106 (1 yr.)  
 David L. Phillips, M.D., 191 Lincoln Ave., Rumford 04276 (1 yr.)  
 Robert F. Ficker, M.D., Maine St., Kennebunkport 04046 (2 yrs.)  
 Hans A. Holzwarth, M.D., 336 Mt. Hope Ave., Bangor 04401 (2 yrs.)  
 Richard M. Swengel, M.D., 477 Main St., Lewiston 04240 (2 yrs.)  
 William O. Buell, M.D., 22 Jefferson St., Box 736, Biddeford 04005 (2 yrs.)  
 Elihu York, M.D., 62 Baribeau Dr., Brunswick 04011 (2 yrs.)  
 T. Craig Childs, M.D., P.O. Box 285, Belfast 04915 (3 yrs.)  
 David G. Reed, M.D., 7 Washington St., Camden 04843 (3 yrs.)

## **Council on Medicine and Law**

#### **Committee on Ethics and Discipline**

John E. Knowles, M.D., 52 Gilman St., Portland 04102 (2 yrs.) — Chairman  
 John C. Van Pelt, M.D., E.M.M.C., Bangor 04401 (1 yr.)  
 Thomas W. Williams, M.D., Penob. Bay Phy. Bldg., Glen Cove, Rockland 04841 (1 yr.)  
 Melvin R. Aungst, M.D., 112 W. Main St., Fort Kent 04743 (1 yr.)  
 Peter F. McGuire, M.D., 56 Baribeau Dr., Brunswick 04011 (2 yrs.)  
 Linus J. Stitham, M.D., 50 Main St., Dover-Foxcroft 04426 (2 yrs.)  
 Waldo A. Clapp, M.D., 215 College St., Lewiston 04240 (3 yrs.)  
 Robert H. Dixon, M.D., 20 York St., Bath 04530 (3 yrs.)

#### **Committee on Legislation**

John P. Dow, M.D., Grove Hill, Pittsfield 04967 (2 yrs.) — Chairman  
 H. Carl Amrein, M.D., 29 Weston Ave., Madison 04950 (1 yr.)  
 James H. Bonney, M.D., 53 Chadwick St., Portland 04102 (1 yr.)  
 Carl E. Richards, M.D., 27 June St., Sanford 04073 (1 yr.)

Brinton T. Darlington, M.D., 89 Hospital St., Augusta 04330 (2 yrs.)  
 Francis I. Kittredge, M.D., 498 Essex St., Bangor 04401 (2 yrs.)  
 Euclid M. Hanbury, Jr., M.D., Medical Bldg., Belfast 04915 (2 yrs.)  
 Kevin Hill, M.D., 325A Kennedy Mem. Dr., Waterville 04901 (3 yrs.)  
 John H. Shaw, M.D., 131 Sewall St., Augusta 04330 (3 yrs.)  
 Martyn A. Vickers, Jr., M.D., 21 Western Ave., Augusta 04330 (3 yrs.)  
 Ulrich B. Jacobsohn, M.D., 130 Main Ave., Farmingdale 04345 (3 yrs.)

#### **Committee on Professional Liability**

Thomas A. Martin, Sr., M.D., 157 Pine St., Portland 04102 — Chairman  
 James H. Bonney, M.D., 53 Chadwick St., Portland 04102  
 George L. Maltby, M.D., 31 Bramhall St., Portland 04102  
 John A. Root, M.D., Penob. Bay Phy. Bldg., Glen Cove, Rockland 04841  
 Allan J. Stinchfield, M.D., 16 E. Chestnut St., Augusta 04330

whose tuberculin skin test is positive. It is anticipated that this will eliminate approximately 70 percent of annual routine chest roentgenograms of residents and 85 percent of employees. On the other hand, the tuberculin skin test program for employees will be strengthened; the program for residents will be continued and closely monitored.

### SUMMARY

Among the 447 residents surveyed at a State residential facility for the mentally retarded in 1974, 131 residents or 29.3 percent (38.1 percent for males and 14.5 percent for females) were positive to the tuberculin test. In 1975, 128 residents or 25.7 percent were positive among 498 tested (31.6 percent for males and 16.2 percent for females). In both years the resident population was almost exclusively white, ranging from 6 years to 75 years of age. There was no true converter in either year. The corrected positivity rates of 26.2 percent in 1974 and 23.9 percent in 1975 appear unusually high and are closer to the figure of 27.8 percent for the household contacts in Maine in 1974 than to the estimated current tuberculous infection rate of 7 percent for the general population of the United States. When the effect of the 1965 tuberculosis outbreak is subtracted, the positivity rates become 19.0 percent (22.4 percent for males and 14.5 percent for females) in 1974 and 17.3 percent (18.1 percent for males and 16.2 percent for females) in 1975. Further corrected rates of 18.4 percent in 1974 and 17.2 percent in 1975 — to

allow comparison with the general population — are closer to 20.6 percent, the positive rate of all the contacts examined in the United States in 1974.

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4. Davidson, D. and Melkis, A.: Tuberculosis Control in Institutionalized Mentally Retarded Patients, *J Maine Med Assoc*, 51 (6): 10-11, 1960.
5. Benson, A. B.: Control of Communicable Diseases in Man, 12 Ed., Washington, D.C., The American Public Health Association, 1975, pp. 340-346.
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10. Horwitz, O. and Darrow, M.: Principles and Effects of Mass Screening: Danish Experience in Tuberculosis Screening, *Public Health Rep*, 91: 146-153, 1976.
11. Committee on Therapy of the American Thoracic Society: Personnel Tuberculosis Control Program in Medical Institutions, *Am Rev Respir Dis*, 104: 463-465, 1971.
12. Tuberculosis Control Division, Center for Disease Control, U. S. Public Health Service: Guidelines for Prevention of TB Transmission in Hospitals, Atlanta, Center for Disease Control, 1974.

## Letters to the Editor

### To the Editor:

The U.S. Public Health Service is preparing to visit Cumberland County to conduct the Health and Nutrition Examination Survey of persons aged 6 months through 74 years. The initial phase will begin on August 1, 1977, with interviewers from the U.S. Bureau of the Census calling on selected households throughout the area to obtain certain demographic information to identify and select about 427 persons for the examination. Examinations will be conducted from August 12 through September 15, 1977, in the survey's mobile examination center.

To assist us in informing physicians about the activities in your area would you please apprise the members of your society about the survey? In addition, if you publish a newsletter or journal, we would appreciate you including a brief description of the program.

The cooperation of the medical profession has contributed to the success of the program in the past. I hope we will be able to rely upon you again. Shortly before we begin actual operations we will send you additional information including the addresses and telephone numbers of our office and mobile examination center. If you have any questions concerning the survey, please contact Mr. Charles Gallese of my staff at 301-443-1626.

DOROTHY P. RICE

Director

Dept. of Health, Education and Welfare  
Rockville, Maryland 20852

### To the Editor:

RE: "Infectious Threats Hide in New Facilities Too"

by Frank W. Kibbe, M.D., Volume 67, November - 1976

In general, Dr. Kibbe is correct when he concludes that there should be some methods established for evaluating and adapting decontamination procedures to new health care facilities before "the doors are opened;" however, there are two areas about which I would like to comment.

Dr. Kibbe implies that persons in the "business" of hospitals are there only for economic reasons and are not on the side of better patient care. In the case of ServiceMaster, nothing could be further from the truth. This is demonstrated by the fact that ServiceMaster is privileged to serve approximately 500 health care facilities. Since the time we became actively involved in health care, over 14 years ago, our acceptance has been dependent on providing high quality, realistic results consistent with better patient care.

Dr. Kibbe also claims that the disinfectant, SaniMaster II,<sup>®</sup> was unable to contain *Pseudomonas* contamination in the nursery and that when a switch was made to another disinfectant, along with a change in procedures, the situation was corrected. The truth of the matter is that most of the "normal" counts were obtained using SaniMaster Phenolic,<sup>®</sup> and not the other disinfectant. Subsequently, SaniMaster II,<sup>®</sup> has also proven effective using the new procedures. This again illustrates the importance of procedure rather than total reliance on a disinfectant.

It is unfortunate and somewhat incredulous that *The Journal of The Maine Medical Association*, which generally enjoys a fine reputation, chose to print this article without demanding rigorous proof of the claims. It should be the duty of authors and publishers to identify the difference between opinion and scientifically validated information. I heartily agree with Dr. Kibbe's own conclusion that "to draw a conclusion from a single experience is not only presumptive, but downright ridiculous."

PHILIP G. PASSON, Ph.D.  
Vice President  
Technical Development  
SERVICEMASTER INDUSTRIES INC.  
2300 Warrenville Road  
Downers Grove, Illinois 60515

#### Reply:

I am pleased that you allowed me to see Dr. Philip Passon's letter prior to publication. I have been away a few months, and thus am rather late in answering.

It is true that SaniMaster Phenolic® was used in certain areas of the Penobscot Bay Medical Center to rectify the high bacterial counts obtained when SaniMaster II® was used, and this is so stated in the article, though the phenolic cleaner is not called by the SaniMaster name. However, Dr. Passon does not give the "truth of the matter" when he states that SaniMaster Phenolic® gave the normal counts in the nursery, particularly the nursery

bench. In this area, during my term on the Infection Control Committee, no SaniMaster Phenolic® was used and Staphene was the cleansing agent employed as stated. The technique was that suggested by Miss Ginsberg of the Bingham Associates and had been used previously at the Knox County General Hospital.

Since Dr. Passon is so concerned that the Maine Medical Journal demand proof of claims, it might be well for him to look to his sources of information, or perhaps it is easier to accept what one wishes to hear if it so fits one's desires, rather than to know the truth.

To comment further on Dr. Passon's remarks concerning business in hospitals, I cannot understand why SaniMaster II® was used in such critical areas as O.R.'s, Delivery Rooms, etc. until the Infection Control group, by monitoring, showed that high bacterial counts were present. Only then did the ServiceMaster Industries suggest switching to their phenolic agent stating that it would probably do a better job, which it did. Why then was it not used originally? Is it maybe more expensive or more trouble to use? Thus, unless a hospital infection officer points out deficiencies, ServiceMaster is willing to go the easier way.

If the J.M.M.A. wishes to check with the bacteriologists: Robert Smith and Pamela Rice concerning the accuracy of the counts and their times, I'm quite sure that confirmation of the studies as described will be forthcoming.

FRANK W. KIBBE, M.D.  
R.F.D. No. 2  
Lincolntonville, Maine 04849

## County Society Notes

### York

The annual meeting of the York County Medical Society and its Auxiliary was held on Wednesday, January 12, 1977 at the Kennebunk Inn, Kennebunk, Maine.

The format consisted of a social hour from 6:30 p.m. to 7:30 p.m. The dinner and separate business meetings followed.

The highlight of this meeting which followed the dinner was a presentation of a magnificent silver bowl, presented by Dr. Owen O. Dow, President of the York County Medical Society, to Dr. Carl E. Richards, which was beautifully engraved as follows, "In appreciation for many years of outstanding service to his town, county and State presented by the York County Medical Society, January 12, 1977." This was truly a well deserved honor. Dr. Richards has been involved in many activities over the years. A few of these are: Past President of the York County Medical Society, Past President of the Maine Medical Association, Past President of the Medical Staff of the Goodall Hospital, member of the House of Delegates of the Maine Medical Association for 35 years and again re-elected this year, formerly a member of the Maine State Board of Registration in Medicine, President of the York County Law Enforcement Association and Deputy Sheriff of York County, member of the American Academy of Family Practice, having served as a delegate and a member of various committees of this group.

Another most interesting feature which took place after this presentation was an outstanding talk by Dr. Robert Wise. His subject was "Medical Travels in the Back Lands of Brazil." This was illustrated by many slides and was tremendously well received by all those present. Dr. Wise is Assistant Chief of Staff, Veterans Administration Center, Togus, Maine; Emeritus Magee Professor of Medicine, Jefferson Medical College, Thomas Jefferson University; formerly Physician-in-Chief, Thomas Jefferson University Hospital, Philadelphia. On completion of his presentation, the business meeting of the Society was called to order by Dr. Owen Dow, President of this Society. The ladies retired for a meeting of their own.

One minute of silence for each was held in respect for the passing of Drs. Oney Smith and Charles W. Kinghorn.

The following is the report of the Nominating Committee for 1977:

President: Dr. Lawrence R. Hazzard, York  
Vice-President: Dr. Thomas Anton, Biddeford  
Secretary-Treasurer: Dr. Melvin Bacon, Sanford  
Executive Committee: Drs. Walter R. Peterlein, Jr., Springvale and Robert S. LaFond, Saco (plus the above 3 officers)

Delegates to the M.M.A. House of Delegates: Drs. Carl E. Richards, Sanford, Robert F. Ficker, Kennebunkport and Michael M. P. Magaouda, Old Orchard Beach. Alternates: Drs. Thomas Anton, Biddeford, Michael J. Festino, Saco and Alvin A. Hoffman, York

Censors Committee: Drs. Marion K. Moulton, West Newfield, Roger J. P. Robert, Biddeford and Paul S. Hill, Jr., Saco  
Peer Review Committee: Drs. Kenneth E. Leigh, York, Harry Lapirow, Kennebunk and Conner M. Moore, Saco  
Nominating Committee (1978): Drs. Melvin Bacon, Sanford, Carl M. Haas, Biddeford and John H. Leonard, York

These were unanimously voted into office by all those present.

The minutes of the last meeting were dispensed with in the interest of time. A very brief financial report was given by Dr. Bacon, Treasurer of York County Medical Society, indicating that we are financially solvent.

Under new business, it was reported that a letter of condolence had been sent by Dr. Bacon, Secretary, to each of the families of Drs. Oney Smith and Charles W. Kinghorn. It was also voted to send a contribution of \$25.00 by the York County Medical Society to each of their favorite charities.

The following announcements were made:

a. The next meeting of the York County Medical Society will be held on Wednesday, March 9, 1977 at the Goodall Hospital, Sanford, Maine.

b. The House of Delegates Meeting will be held Sunday, March 27, 1977 in Bangor, Maine.

A report of the House of Delegates Meeting held at the Mid-Maine Medical Center at Waterville, Maine on December 12, 1976 will be given at the March meeting.

Under correspondence, it was reported that a letter had been received from Dr. Brinton T. Darlington, Chairman of the Legislative Committee, requesting members of our Society to contact members of the State legislature regarding information of perti-

nence to physicians.

A letter was also received regarding a combined meeting of members of the Maine Bar Association and members of the York, Cumberland, Sagadahoc, Androscoggin and Oxford County Medical Societies. Dr. Dow delegated your secretary to help expedite this meeting.

Lest we forget, mention should be made of a gift bag that was presented to each of the ladies present.

Meeting adjourned at 10:30 p.m.

The March meeting of the York County Medical Society was held on Wednesday, March 9, 1977 at the Goodall Hospital, Sanford, Maine. The program consisted of a social hour beginning at 6:30 p.m., dinner at 7:30 p.m. and the business meeting following.

The business meeting which followed the excellent dinner was conducted by Dr. Melvin Bacon, Secretary, in the absence of the President and Vice-President. He introduced the speaker who was Stanley Hanson, Executive Director of the Maine Health Systems Agency, Augusta, Maine. His subject was "General Analysis of the Health Systems Agency Toward the Medical Profession." It was a most interesting and informative talk which was replete with questions and answers. Comment should be made regarding the consensus of opinion of the physicians present that they would be willing to make house calls if they were paid the same fee as allowed the members of the Visiting Nurses Association.

The minutes of the last meeting were dispensed with in the interest of time. There was no old business. The application for membership in the York County Medical Society by Dr. Harlow B. Rowell of York, Maine was accepted and approved.

The following announcements were made:

a. The next meeting of the York County Medical Society will be held on Wednesday, May 11, 1977 at the Webber Hospital, Biddeford, Maine.

b. A joint meeting of the Maine Bar Association and the Maine Medical Association including York County will be held on Wednesday, March 16, 1977 at the Red Coach Grill, Portland, Maine.

c. The Interim Meeting of the House of Delegates of the Maine Medical Association will be held at the Eastern Maine Medical Center in Bangor on Sunday, March 27, 1977 with registration at 12:30 p.m.; dinner at 1:00 p.m. and business meeting at 2:00 p.m.

d. A meeting on "Alcoholism" will be held at the Goodall Hospital on Saturday, April 23, 1977.

A report was given by Dr. Maurice Ross of the Executive Committee meetings and the House of Delegates' meeting held on December 12, 1976 at Waterville, Maine.

Correspondence read included a letter from the York Hospital concerning Dr. Kinghorn, a letter from the University of Vermont in regards to Dr. Oney Smith and also a letter from the family of Dr. Smith. There was also a letter read from Dr. Hanley requesting names of physicians who have not been able to secure Malpractice Insurance.

The meeting was then adjourned.

There were 12 physicians and 2 guests present. We were all appalled with the paucity of physicians in attendance. All those present considered this meeting worthwhile.

MELVIN BACON, M.D., *Secretary*

### Penobscot

The February meeting of the Penobscot County Medical Society was held on February 15, 1977 at the Pilots Grill in Bangor, Maine.

The meeting was opened by the President, Dr. John A. Woodcock. Due to the inclement weather, it was decided to reverse the order of the meeting and present the speaker first and hold the business meeting later.

Dr. Richard C. Leck, President of the Maine Medical Association, presented an enlightening overview of the current problems the M.M.A. is facing, both short range and long range. Regarding short-range problems, Dr. Leck outlined the difficulties involved in finding a replacement for Dr. Hanley, as well as finding a new home base for the Association. He also discussed the possible change in the statute of limitations in regard to malpractice liability.

In regard to long-range problems, that of a possible National Health Insurance and Certificate of Need legislation were discussed. He warned of potential regimentation of medical care. He further encouraged us to become the patient's advocate so that we could have society on our side as the government tends to invoke further controls on our practice. An interesting question and answer period followed the formal talk.

The business meeting was then resumed by President Woodcock and the minutes of the previous meeting were discussed and approved.

Under old business, Dr. Woodcock noted that the plans for the combined meeting with the Maine Bar Association in April are progressing; this meeting is to be held at the Pilots Grill.

Under new business, a recent letter from the Bangor area legislators regarding the potential closing of the Bangor Mental Health Institute was discussed. Prior to the main meeting, the Executive Committee of the Society decided to send a copy of last October's communication to Governor Longley regarding the support of the Penobscot County Medical Society in retaining BMHI, to the Chairman of the Appropriations Committee and Health and Institutional Care Committees in both the House and Senate and also to the Bangor area legislators.

The communication from Dr. Hanley regarding malpractice insurance was discussed. The County Society membership was encouraged to notify the secretary of any problems in obtaining malpractice insurance so Dr. Hanley can be informed within the next six weeks. A letter to all County Society members inquiring of such problems will be sent.

Applications for membership in the County Society for Drs. William B. Watt and Edward M. Harrow were unanimously approved. The application for transfer from the Aroostook County Society to Penobscot County Society for Dr. G. Vernon A. MacDonald was also approved.

As there was no further business, the meeting was adjourned at 9:30 p.m.

The March meeting of the Penobscot County Medical Society was held on March 15, 1977 at the Airport Hilton in Bangor, Maine.

The meeting was opened by the President, Dr. John A. Woodcock. In view of the distance our speaker needed to travel after the meeting, it was decided to reverse the order of business and present the speaker first and have the formal business meeting thereafter.

Guests to the meeting, Senator Pierce of Waterville and Representative Tarbell of Bangor were introduced. Charles L. Cragin, III, the lobbyist for Maine Medical Association in the State Legislature and a member of Verrill and Dana Law Offices of Portland, then spoke to us regarding recent legislative activities in Augusta and some of the more important proposed bills. A considerable portion of his talk was devoted to the malpractice problem in the State of Maine. He noted that L.D. 149, that relating to the Joint Underwriting Association, was recently passed; this provides for a two-year extension of the Association which, with the removal of the Exclusivity Provision, would enable physicians to obtain malpractice insurance throughout the State if they have not been able to obtain such in the private sector. Mr. Cragin further summarized the report to the legislature of the Pomeroy Commission regarding recommendations to revise the laws as they are related to medical and hospital malpractice insurance in the State; this has become L.D. 727 to be acted upon in this session of the legislature. He noted that the M.M.A. supports this bill in its entirety and he urged us to become familiar with its contents (copies of the report have been distributed to the physician roster of the State.) A public hearing on this bill is planned within the month and Mr. Cragin urged our attendance as the bill very significantly affects the individual physician in regard to his relationship with the patient as well as overall malpractice. Peer review, immediate "incident reporting," the relationship between provider and insurance carriers and the very important arbitration procedure to replace the trial system were noted to be some of the highlights in the commission's report. Also the good samaritan concept, informed consent and ninety day notice to the physician prior to actual serving of a lawsuit, were also noted to be general provisions of the

report. Mr. Cragin then outlined some of the other bills presently before the legislature: the certificate of need legislation, rate review legislation as it pertains to hospitals, the "living will act" (L.D. 184), and the bill L.D. 311, regarding postgraduate medical education in the State. This latter bill, proposed by Senator Pierce, will provide Maine residents with openings at the University of Vermont and Tufts University Medical School for those individuals who were not able to gain admittance on their own. This would entail the first two years at either of those two schools and the clinical years within the Maine hospital system. The funding is to be through the State, and should the graduate return to Maine for practice, the requirement for repayment of the funds would be eliminated. It was finally noted that the "living will act" (L.D. 184) will in all probability not pass legislation; it was thought to be unnecessary legislation by the M.M.A. and that such decisions regarding the medical care of patients in a terminal state were being appropriately carried out by and large throughout the State anyway, without such a law. A lengthy question and answer period followed the formal talk.

The business meeting was then resumed by President Woodcock and the minutes of the previous meeting were discussed and approved.

Under old business, replies from several State legislators regarding our letter last month that expressed the Society's opinion to retain BMHI were noted. Each reply appreciated our concern and opinion and encouraged such communication.

It was also noted that several replies from Penobscot County physicians in regard to difficulties in obtaining adequate malpractice insurance had been received by the Secretary's office as so requested in a letter to County Society members last month. Plans are to notify Dr. Hanley of these problems by early next month so that the Joint Underwriting Association Provisions might be enacted to help these physicians to obtain the proper insurance.

Under new business, a communication from Dr. Barrett of March 3, 1977 was read; this letter expressed his concern regarding the lack of involvement by the County and State Medical Association in L.D. 184 (living will act). The recent developments in regard to this act as noted by Mr. Cragin will be communicated to Dr. Barrett.

Finally, it was announced by Dr. Woodcock that the plans for the combined meeting with the Maine Bar Association in April are being finalized; this is to be held at the Red Lion Restaurant on April 19, 1977.

As there was no further business, the meeting was adjourned at 10:00 p.m.

H. CLEMENT JURGELEIT, M.D., *Secretary*

### Androscoggin

The Androscoggin County Medical Association held its March meeting on March 17, 1977 at the No Tomatoes Restaurant in Auburn, Maine, with 54 members present and five guests.

The meeting was called to order by the President, Dr. Charles Hannigan at 7:10 p.m.

The secretary's report was given by Juliette Giguere, secretary protem. The report was accepted as read and placed on file.

Correspondence was read from Dr. Michael C. Bach and Dr. George E. Davis, Jr. regarding their resignation on the AD HOC Committee. The resignations were accepted and discussion of the committee followed.

The request for transfer of membership of Dr. George E. Davis, Jr. from Androscoggin County to Kennebec County was authorized.

Drs. Mark M. Eule and Leo Cousineau were presented for acceptance to membership. Both were voted to membership and welcomed to the Androscoggin Association.

The application of Dr. Alan S. Rogers was referred to the credentials committee.

A resolution proposed by Dr. Frederick C. Holler, regarding the implementation of the Emergency Telephone number 911, was read and discussed. The motion was made by Dr. Holler and duly voted by the membership. The secretary was instructed to send a copy of the resolution to City officials, Mayors of Lewiston and Auburn, Chairman of both City Councils, Chiefs of both

the Fire Departments and Police Departments, as well as the Sheriff of Androscoggin County for the County Commissioners.

A resolution prepared and proposed by Dr. Robert F. Kraunz regarding the banning of the use of Saccharin was read and discussed. Following discussion, it was voted to accept this resolution with a copy to be sent to U.S. Senator Ed Muskie, U.S. Senator William Hathaway and both U.S. Representatives, Bill Cohen and David Emery.

The next item of new business was the report of a suggestion by Pat Archambault that we hold guest night at Martindale Country Club instead of No Tomatoes. Tentative date is Saturday, May 21, 1977. Mr. Archambault said one week's notice would be sufficient to prepare catering. Dr. Jou Tchao, solicited the audience for suggestions for a program for ladies' guest night; no suggestions were offered.

Dr. Tchao introduced a panel of Mr. Paul Sarbello, Consultant in Professional Management of Boston, Mr. Dermott Healey, CLU, expert in Estate Planning of Longley Associates and Attorney Bryan Dench who reviewed New Tax Laws as it affects the physician's practice and his estate. The matter reviewed was most enlightening. A question and answer period followed.

Dr. Tchao thanked the panelists.

Next meeting at No Tomatoes on Thursday, April 21, 1977.

Meeting adjourned at 9:40 p.m.

JULIETTE A. GIGUERE, R.N., *Secretary protem*

The April meeting of the Androscoggin County Medical Association was held at No Tomatoes Restaurant in Auburn, Maine on April 21, 1977. The business meeting was preceded by a social hour and dinner.

The business meeting was called to order by the President, Dr. Charles Hannigan, with 45 members present and one guest.

A Eulogy and Resolution on the passing of our colleague, Dr. Donald Anderson, were presented. It was voted to make this resolution part of the minutes of this meeting and that a copy be sent to the family and to the Maine Medical Association. A moment of silence was observed in respect of our distinguished departed member.

The minutes of the March meeting were accepted as read and placed on file.

The application for membership of Dr. Alan Rogers was presented and duly voted upon. Dr. Rogers was welcomed into the County Association and the Maine Medical Association.

Under correspondence, letters acknowledging the resolution submitted regarding the banning of the use of Saccharin were read, from Senator Muskie and Senator Hathaway.

Dr. Thomas F. Shields reported on the last meeting of the House of Delegates of the Maine Medical Association. A discussion of the State budget followed. Dr. Shields also reported on the resolution of the Executive Committee and on the resolution of Kennebec County Medical Association.

Reports of special committees: Dr. Norman O. Gauvreau reported on the AHEC Committee. Two meetings were held with administrators of both hospitals. Dr. Margaret H. Hannigan attended a meeting in Bangor and reported that we were fourth place with Bangor first, then Portland, Waterville and then Androscoggin County. Dr. Hannigan said Bangor meeting pushed for prestige, money and program. We should suggest two more members for the committee prior to July 5th. Logical candidates should be brought to the State Board. The committee now has eight members: Drs. Charles Hannigan, Jou S. Tchao, Stanley D. Rosenblatt, John W. Carrier, Jon P. Pitman, Lawrence A. Nadeau, Norman Gauvreau and Leo E. Cousineau. Dr. Charles Hannigan suggested that a meeting with Dr. Manu Chatterjee for this County would be profitable. A motion by Dr. Gauvreau for hiring a joint Medical Education Director for the County was discussed and duly voted by the membership.

Any member interested in serving on the Blue Cross-Blue Shield Board should make their wish known to the secretary.

Dr. Charles Hannigan reported on several matters presently before the Legislature: The matter of the Medical School vs. Compact Plan was reviewed, the Nurse Practice Act, prenatal determination of sex, the matter of pronouncing a deceased patient within 48 hours. Dr. Hannigan encouraged the members to take special attention to these matters under consideration.

Dr. Thomas Shields presented two motions for Resolutions to the Maine Medical Association:

1. Moved: No later than January 1, 1979, to acquire or rent buildings in Augusta, Maine, for the transfer of the headquarters of the Maine Medical Association to Augusta, Maine by that date.

2. Moved: To amend the Bylaws of the Maine Medical Association, Chapter IV, Section 10, with the addition of "except those nominated as a District representative to the Executive Committee."

This now reads as follows:

Section 10, "Any delegate may make further nominations for any office within the power of the House of Delegates to elect."

These resolutions were discussed and voted on unanimously.

A fine presentation of the Social System of the practice of medicine in Canada was given by Dr. Victor M. Parisien and Dr. Leo E. Cousineau. This system is based on the British system.

It was voted that Dr. Charles Hannigan make arrangements for the ladies' night meeting on May 19th.

Meeting adjourned at 10:20 p.m.

FREDERICK B. LIDSTONE, M.D., *Secretary*

#### Franklin

A meeting of the Franklin County Medical Society was held on April 11, 1977.

The meeting was called to order by the President, Dr. Paul A. Brinkman.

Report by Dr. Daniel K. Onion of activities at House of Delegates meeting with presentation of Maine Medical Association budget, presentation of the contingency plans involving Dr. Hill assuming Dr. Anderson's duties as President-elect and presentation of the resolution to extend the term of past Medical Association presidents on the Executive Committee to a total of three years after their year of presidency. The membership voted to ask its delegates to support the current system rather than extend past presidents' terms on the Executive Committee any further so as not to dilute regional representation on the Executive Committee.

DANIEL K. ONION, M.D., *Secretary*

#### Kennebec

The Kennebec County Medical Association met at the Silent Woman in Waterville, Maine on April 21, 1977 with 19 members present.

The speaker for the evening was Mr. Stanley Hanson and his associate from the Maine Health Systems Agency.

Variable business was conducted and Dr. Alice Feniquito was elected to membership.

Dr. Martyn A. Vickers, Jr. volunteered to run for the Presidency of the Maine Medical Association in the absence of a President-elect as a result of the tragic death of Dr. Anderson. The members of the Society who were present voted to endorse Dr. Vickers and to support his candidacy.

O. THOMAS FEAGIN, M.D., *Secretary*

**MEDICAL DIRECTOR:** The Pine Tree Organization for Professional Standards Review, Inc. is seeking a Medical Director to assist in the implementation of Maine's PSRO program by being responsible for all matters of a medical review nature, acting as liaison between the State's medical societies and all organized peer review committees and the PSRO program, assisting in the development of standards and criteria for review of the quality of medical care in Maine, and assuring broad-based physician involvement. Salary range is approximately \$40 K. For job description and information on salary and fringe benefits, send curriculum vitae to: Ronald G. Thurston, Executive Director, Pine Tree Organization for Professional Standards Review, Inc., P.O. Box 706, Augusta, Maine 04330.

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# The Journal of the Maine Medical Association

Volume Sixty-eight

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Number 9

## The Place of Surgery in the Treatment of Ischemic Brain Disease

### A Thirteen-Year Experience Based on Ninety-Two Carotid Endarterectomies

JEREMY R. MORTON, M.D. and CLEMENT A. HIEBERT, M.D.

As many as 75% of patients with ischemic strokes have a surgically remediable stenotic lesion in an extracranial artery; usually the site is the carotid at its bifurcation.<sup>1</sup> In most instances the *intracranial* vessels are surprisingly free of occlusive disease. Although a debilitating stroke may occur as the first sign of extracranial cerebrovascular disease, more often these patients have one or more premonitory episodes of transient neurologic or visual symptoms. If these symptoms are recognized and the vascular lesion is defined and corrected promptly, it is believed that many tragic strokes may be averted.

The purpose of this paper is to review clinical features of extracranial cerebrovascular disease and to present a thirteen-year personal experience with ninety-two carotid endarterectomies.

An atherosclerotic plaque at the carotid bifurcation may manifest itself either by limiting the flow of blood to the brain or by producing small platelet or cholesterol emboli which obstruct small arterial branches in the brain or in the retina. Clinical manifestations include:

#### TRANSIENT LIMB WEAKNESS

Transient episodes of unilateral limb weakness, sometimes accompanied by aphasia, suggest the presence of a flow limiting stenotic lesion of the contralateral carotid artery. These episodes, often referred to as transient ischemic attacks or "TIAs", last from a few minutes to a few hours. If the symptoms last longer than this, the episode is considered to represent a small completed stroke and is treated accordingly. Weakness in the arm is usually

more pronounced than in the leg and dizziness may or may not be present. Transient aphasia may occur alone or accompany limb weakness, particularly when the weakness involves the right side of the body.

#### VERTEBRAL-BASILAR SYMPTOMS

Occasionally patients experience transient episodes of vertigo, staggering gait, diplopia, or bilateral visual field defects. The visual symptoms are often described as a "curtain" moving briefly across the field of vision. These symptoms suggest the presence of a flow limiting arterial lesion of the posterior circulation and might be anticipated in a patient with vertebral artery stenosis. In actual practice, however, because of the multiple intercommunications between the anterior and posterior cerebral circulation, patients with these symptoms are usually found to have stenotic lesions of both the carotid and vertebral arteries. Surgical correction of the carotid stenosis alone will in most instances eliminate the symptoms.

#### TRANSIENT UNILATERAL BLINDNESS (AMAUROSIS FUGAX)

Transient monocular visual loss may be partial or complete and may be only a momentary dimming of vision in one eye. These symptoms are produced by tiny emboli formed in ulcerated or irregular plaques at the carotid bifurcation which subsequently find their way into the retinal vessels of the ipsilateral eye. If left untreated, these ulcerated plaques may in time produce larger emboli resulting in permanent loss of vision or stroke.

### TRANSIENT NONSPECIFIC NEUROLOGIC SYMPTOMS

Vague or nonspecific symptoms such as, dizziness, transient numbness of an extremity, or blurring of vision are particularly difficult to evaluate relative to cerebral vascular disease. Although the temptation is to disregard symptoms of this type, like the others these may represent the only warning signs of impending stroke. If accompanied by a carotid bruit, one should assume for purposes of work-up that these symptoms are related to carotid disease.

### THE CAROTID BRUIT

Although the carotid bruit is an important physical sign, it is by no means diagnostic. Loud bruits may be caused by ectatic vessels or stenosis of the external carotid artery with a widely patent internal vessel. Similarly a subtotally occluded internal carotid may produce little or no bruit, and of course, the totally occluded internal carotid produces no bruit. Therefore, although bruits in the neck frequently denote significant obstructive carotid disease, they are certainly not diagnostic.

### ANGIOGRAPHY

In addition to a complete neurologic examination, the majority of these patients should have an electroencephalogram and a brain scan to rule out the possibility of cerebral infarct, tumor, or hematoma. It is generally accepted that any patient with transient symptoms suggesting cerebral vascular disease with or without a bruit in the neck should undergo arteriography using the retrograde transfemoral technique. In expert hands this procedure is attended by an extremely low mortality and morbidity.

During the past five years at the Maine Medical Center, 666 arteriographic examinations have been performed for suspected extracranial cerebral vascular disease. Of these, 609 were arch studies and 57 selective carotid arteriograms. Out of this group, one patient suffered a severe stroke during the angiogram and subsequently died. Three patients developed a hemiparesis, two of which cleared completely within forty-eight hours. The remaining patient was left with some residual weakness at the time of discharge. One additional patient suffered an increase in the size of an existing area of blindness in one eye. This represents a mortality of 0.15%, a transient morbidity of 0.45%, and a permanent morbidity of 0.15% associated with angiography.

### SURGERY

A stenotic lesion of an artery which narrows the luminal diameter by 50% produces a 75% reduction in cross sectional area. Stenoses of this magnitude and greater are associated with a pressure gradient and a significant reduction in flow through the vessel.

An artery with a lesser degree of stenosis but with

an irregular or ulcerated plaque can be the source of repeated emboli to the brain or to the eye.

Having established the presence of a stenotic or ulcerated plaque as the probable cause of a patient's symptoms, one should proceed without undue delay to endarterectomy of the involved vessel.

Carotid endarterectomy is performed through an oblique incision along the anterior border of the sternocleidomastoid muscle. This requires about an hour of operating time and is a remarkably benign operation in terms of postoperative pain and morbidity. Patients are usually up and about on the first day and home by the fourth or fifth day. The procedure does involve manipulation of the carotid artery and temporary interruption of its blood flow. There is, therefore, a small but definite risk of an intraoperative neurologic complication, ranging from transient weakness of a limb postoperatively to complete hemiparesis in very rare instances.

The incidents of intraoperative neurologic complication varies significantly from one center to another.<sup>2</sup> The results of our experience are presented below.

During the past thirteen years, ninety-two carotid endarterectomies have been performed at the Maine Medical Center by the authors, eighty-one of these in the past six years. The mean age was sixty-four years with twenty-two patients over seventy and five over eighty. Symptoms consisted of TIAs in fifty-nine, amaurosis fugax in thirty-eight, mild completed stroke in sixteen, acute stroke in two, and dizziness in twenty-one. Eleven patients were diabetic, twenty-seven hypertensive, and sixty-three had evidence of coronary or peripheral vascular disease.

Fifteen patients had significant obstructive disease of both internal carotid arteries and eleven of these underwent staged bilateral endarterectomy. Twelve patients had an occluded internal carotid on one side and a severe stenotic lesion on the other. In each instance, the stenotic vessel alone was corrected.

Endarterectomy without an inlying shunt and with simple closure of the artery was performed in most instances. In twelve cases with particularly widespread cerebrovascular disease, a shunt was employed and in seven patients a vein patch was used to widen the arterotomy closure.

There was one hospital death; this occurred early in the series in a patient operated for acute stroke with a totally occluded carotid. Postmortem examination demonstrated a hemorrhagic cerebral infarct. Because of similar experiences elsewhere,<sup>3</sup> patients with an acute stroke are no longer considered surgical candidates.

Four patients in the series suffered transient neurologic deficits following operation. Three of these were patients in whom a shunt was used, and one was a patient with a postoperative hypertensive crisis secondary to renovascular disease.

No patients operated for asymptomatic bruit or transient ischemic symptoms suffered any permanent neurologic sequelae following surgery. Two patients, who had suffered previous strokes, left the hospital with increased neurologic deficits related to surgery.

### RESULTS

Follow-up information was obtained from the referring physician of all but five of the patients. Five patients have died, two probably of stroke and three of unrelated cause. Six patients developed single transient neurologic episodes from two weeks to three years postoperatively. These ranged from transient aphasia to amaurosis fugax and did not recur following institution of antiplatelet medication. Two other patients were restudied because of recurrent transient symptoms, one at three years showed an occluded common carotid artery and the other at one year showed no significant pathology.

Two patients have returned at two and three years with transient symptoms on the opposite side and have undergone a second endarterectomy.

One patient developed recurrent obstructive disease ten years after his long and extensive endarterectomy.

One patient developed recurrent obstructive disease ten years after his long and extensive endarterectomy for a totally occluded artery. Repair of this badly diseased vessel was difficult and intraoperatively the patient developed a severe hemiparesis and several months later expired. Thus of eighty-four patients on whom there is follow-up information (one to thirteen years) and who have not died of unrelated causes, three patients (3.5%) have had fatal strokes and eleven recurrent neurologic symptoms. In only two (2.4%), however, did the recurrent symptoms not resolve with appropriate therapy.

### ASYMPTOMATIC BRUITS

Perhaps the most controversial area in carotid surgery concerns proper treatment of asymptomatic

carotid bruit. In an effort to resolve this issue Thompson, et al.<sup>4</sup> have followed a group of two hundred and twenty-one patients with asymptomatic bruits over ten years. Approximately half of these patients were treated without surgery of which 54% remained well, 27% developed TIAs, and 19% had fatal strokes. The other half of the group underwent endarterectomy. In this half there were no deaths, two patients developed a neurologic deficit related to surgery (1.7%), and two suffered long-term nonfatal strokes (1.7%).

It would appear from these figures, therefore, that in nearly half of the time the asymptomatic bruit is not an innocent lesion. Since in very experienced hands, carotid arteriography can now be performed with mortality and serious morbidity, each less than 0.2%, consideration should be given to studying some of these patients with asymptomatic bruits. If a critically stenotic lesion is discovered in a patient about to undergo a major surgical procedure then certainly carotid endarterectomy should be performed first. If other surgery is not contemplated, then the decision regarding endarterectomy might be cautiously considered based on the condition of the patient, the severity of the lesion, and the experience and previous results of the surgeon.

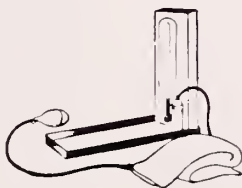
### ACKNOWLEDGEMENT

The authors gratefully acknowledge the assistance of Karen Tolan in preparation of the statistical material.

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Drs. Morton and Hiebert, 321 Brackett St., Portland, Maine 04102



# Suture Line Recurrence Following Resection of Left Colon Carcinoma: Maine Medical Center Experience

RICHARD C. FLAHERTY, M.D. and GEORGE F. SAGER, M.D.

The development of a suture line recurrence of tumor following resection for carcinoma of the large intestine is a serious problem which may compromise an otherwise curative resection. Its incidence and pathophysiology have been debated in numerous papers, as have the many techniques purported to prevent this complication. It is the purpose of this paper to review this problem and to present the incidence of suture line recurrence at the Maine Medical Center for the fifteen-year period, from 1961 to 1975.

Four theories as to the etiology of suture line recurrence following resection of the large intestine for cancer have been advanced: 1) implantation of viable luminal tumor cells by suture; 2) the adherence of tumor cells to viable cut ends of bowel; 3) local metastases; 4) recurrence from residual tumor, i.e., tumor in the resected margin. The suture implantation theory views the mechanism of recurrence as being caused by the suture itself.<sup>1,2</sup> The intestinal mucosa, with its constant shedding of cells normally acts as a barrier to the implantation of tumor cells which have been shed from the tumor mass and lie free in the bowel lumen. As the suture passes through the bowel wall, it breaks this barrier and carries the viable tumor cells with it into the submucosal and muscularis layers where the proper nutritional milieu for tumor cell growth exists. The second theory<sup>3</sup> is similar in that it views the inverted viable cut ends of bowel as being an hospitable environment onto which the shed tumor cells can adhere and grow. The third theory considers a suture line recurrence as being caused by a "local metastasis."<sup>4</sup> Here, there are thought to be numerous tumor cells in the fine reticular lymphatic systems which exist in the various layers of the bowel wall. These cells are most numerous close to the tumor site but some cells are found at a considerable distance from the area of resection at the time of surgery. Most of these cells die, but some survive and become implanted at the site of resection where the lymphatic flow is obstructed. There they grow to constitute a macroscopic recurrence. The fourth theory is that of inadequate initial resection with tumor present either in the resected margin, or in an

area adjacent to the bowel wall which simply grows at the margin of resection, i.e., the suture line. Manson<sup>5</sup> reports that the rate of recurrence is constant until a margin of 7 cm is reached. He found no recurrence with margins over 7 cm. This seems to support the theory. However, he failed to find a recurrence of cancer in two patients who had a distal margin of resection involved with cancer. The first two theories are dependent on the presence of viable luminal tumor cells. The third and fourth theories are dependent on the margin of resection.

There have been many experimental studies which have been performed in an attempt to prove one or the other of the above theories as being the correct one. Most of these have been performed on experimental animals. Typical studies have consisted of the preparation of a solution of tumor cells, isolation of a segment of intestine, injection of the cells into the intestinal segment, and then performing an anastomosis on the segment. With such a model, closed intestinal anastomoses (in which the suture does not enter the lumen of the intestine) have been shown to be superior to open anastomoses, supporting theory #1.<sup>1,2</sup> Devitalizing the cut ends of bowel has been shown to decrease the instance of suture line recurrence, supporting theory #2.<sup>3</sup> The use of various intraluminal agents to kill viable tumor cells has been shown to reduce the incidence of suture line recurrence, supporting both theories #1 and 2.<sup>6,7</sup>

## EXPERIENCE AT THE MAINE MEDICAL CENTER

A retrospective review of the tumor registry records made for the period 1961 to 1975 disclosed the records of 441 patients who had an operative procedure for a carcinoma of the left side of the colon. Operations done for rectal lesions were excluded. This study was confined to the left side because of the well recognized higher incidence of suture line recurrence in this location.

Of these 441 patients, 236 were selected out for analysis. These patients met the following criteria: a Dukes' A, B, or C lesion; no evidence of perforation pre-operatively; a minimum follow-up of 5 months (the range was 5 months to 16 years — the average was 5.0 years); the surgery included a resection and primary anastomosis. Fifty-one of these 236 patients had a recurrence of their tumor. Thirty-eight of these 51 had hospital records or private physician records available for review. The

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TABLE 1

188 ANTERIOR RESECTIONS UNDERTAKEN FOR CURE  
(SIGMOID AND RECTOSIGMOID LESIONS)

Classification		No. of Cases	No. of Suture Line Recurrences	%
Dukes'	A	17	0	0
	B	127	5	3.9
	C	44	2	4.5
	Total	188	7	3.7
Broder's	I	3	0	0
	II	85	4	4.7
	III	59	1	1.7
	IV	0	0	0
	Unspecified	41	2	4.8
Total		188	7	3.7

other 13 had no follow-up records available. These latter patients did have a recorded recurrence in the tumor registry files, but the site of the recurrence was not specified. Seven of the 38 (18.4%) with follow-up records available had a recurrence at the suture line. The overall incidence of known suture line recurrence was 7/236 or 3.0%. Assuming that the incidence of suture line recurrence was the same in those 13 patients with unavailable follow-up records as in the others, i.e., 18.4%, the overall projected incidence of suture line recurrence in this group would be 4.0%.

An analysis of those 7 patients who had a suture line recurrence is as follows. The time from initial surgery to recurrence varied from 5 months to twenty-six months with an average of 16 months. In other studies,<sup>8</sup> the vast majority of suture line recurrences has occurred within 3 years of the initial resection. Two were categorized as having a Dukes' C lesion and 5 had a Dukes' B lesion. The length of the distal margin varied from 2.5 to 5 cm with an average of 3.7 cm (in one specimen the length was not specified). Manson, et al<sup>5</sup> had reported that in their experience the rate of recurrence seems to be constant up until the distal margin of 7 cm is reached. In our patients all had a distal margin of less than this. It should be noted that the measurements done in the pathology laboratory average approximately 40% less than those done at the time of surgery.<sup>8</sup> The distal margins in our series were as measured in the Pathology Department. Manson does not specify where the margins in his study were measured. All 7 anastomoses were performed at or below the peritoneal reflection; all were low anterior resections (only one side of the anastomosis consisted of the peritonealized bowel); and all anastomoses were open and two-layered. There was little association between Dukes' staging, Broder's histological grading and the recurrence of tumor (Table 1).

To ascertain the rate of suture line recurrence in the group at highest risk, i.e., those with sigmoid and rectosigmoid lesions, we analyzed these separately. One hundred eighty-eight cases of the above mentioned 236 cases had lesions in the sigmoid colon or at the rectosigmoid junction and underwent

an anterior resection. All 7 suture line recurrences occurred in this group. Thirty-nine of these 188 patients had a recurrence according to the tumor registry files. Twenty-eight of these 39 had hospital records or private office records available for review. In all, 7/28 (25%) recurrences following anterior resection for sigmoid or rectosigmoid lesions were at the suture line. The known incidence of suture line recurrence was 7/188 (3.7%). The projected incidence of suture line recurrence was 5.2% in this group (Table 1).

## DISCUSSION

There have been several recent reports from large surgical centers regarding the incidence of suture line recurrence in anterior resection for sigmoid carcinoma. The Lahey Clinic experience<sup>5</sup> with 152 patients who had a resection and anastomosis at or below the peritoneal reflection included 133 with Dukes' A, B, or C lesions, who thus had an attempt at curative resection. Thirteen of these 133 patients had a recurrence of their tumor at the suture line. This represents a suture line recurrence rate in this series of 9.8%.

The Mayo Clinic experience<sup>9</sup> with this problem was quite similar to our own. They divided their patients with sigmoid carcinoma into two groups, those patients with lesions above 20 cm and those patients who had lesions from 6 to 20 cm. All of these measurements were measured from the dentate line. Their experience with the lower group was 32 suture line recurrences/556 patients or 5.76%. In the higher group the rate was 10/346 or 2.89%. Their overall rate of suture line recurrence in sigmoid resections undertaken for cure was 42/902 or 4.66%.

The Cleveland Clinic experience, reported by Dr. Turnbull,<sup>10</sup> over the past five years has been different. The use of radical local resection, irrigation of the lumen of the intestine with a 40% alcohol solution (recovered via an inlying Pezzer catheter in the rectum), in approximately 350 resections per year, has been followed by no suture line recurrences. The only recent suture line recurrences at that institution have been associated with the use of a stapling device for anastomosis in low lying lesions.

In any individual case of a recurrence at the suture line, any of the four mechanisms mentioned at the onset of this paper may be operative. Perhaps the best course of action in performing a colonic anastomosis for cancer is irrigation of the bowel lumen with a cytotoxic agent and wide local incision of the tumor. These two factors would recognize the importance of all four proposed mechanisms. Using these principles, Turnbull has found the incidence of suture line recurrence to be all but nonexistent.

In most studies<sup>11,12,13</sup> the site of suture line recurrence has shown a dramatically high predilection for the left colon. It has been stated that the incidence of suture line recurrence increases as the tumor site becomes more distal.<sup>8</sup> The cause of this is unknown

but there have been several possibilities put forth. The rectosigmoid acts as a reservoir for desquamated viable tumor cells as well as feces. The increased number of viable luminal tumor cells, together with the added amount of manipulation necessary for resection of low lying lesions may be major factors. In addition, it is also difficult to obtain adequate margins of resection in low lying lesions. Differing local immune factors in the left colon as opposed to the right colon may also be involved. Cleveland's studies<sup>14</sup> with rabbits showed a much higher incidence of suture line recurrence following colocolonic anastomoses as opposed to ileocolonic anastomoses in a controlled experimental setting. Wright<sup>15</sup> confirmed this in a retrospective clinical study.

There have been several factors which have been shown to have increased the incidence of suture line recurrence in animal and in limited human studies. Among them are the following. Preoperative antibiotic bowel preparation has been reported to result in an increased incidence of suture line recurrence.<sup>8,13</sup> Open intestinal anastomoses have been shown in experimental animals to result in more frequent suture line recurrence as opposed to closed anastomoses for reasons previously mentioned.<sup>2</sup> In addition, vigorous handling of the tumor intraoperatively is thought to cause increased shedding of tumor cells.

Various techniques have been used to decrease the incidence of suture line recurrence. These include: closed intestinal anastomoses; denaturation of the surface cells of the inverted cut ends of bowel (in experimental animal studies only 10% formalin solution is found to be significantly effective<sup>3</sup>); isolation of the involved colonic segment with umbilical tapes; iodized catgut suture<sup>1</sup> (the iodine will kill any tumor cells coming into direct contact with it and thus prevent implantation via suture); various intraluminal chemical irrigants (including) chlorthalidone,<sup>8,16</sup> Dakin's Solution,<sup>16</sup> mercury bichloride,<sup>6,17</sup> 5-fluoro uracil,<sup>7,18</sup> nitrogen mustard<sup>18</sup> and 40% alcohol solution<sup>10</sup>). Low molecular weight Dextran has been used as an intraperitoneal irrigant to decrease the adsorbability of any tumor cells spilled in surgery.<sup>1</sup>

### SUMMARY

The Maine Medical Center experience with suture line recurrence following resection of left colonic lesions with anastomosis over the period 1961 to 1975 indicated an incidence of 4.0%, and is most frequent in low sigmoid lesions. In sigmoid resec-

tion the incidence was 5.2%. All of our recurrences appeared at or below the peritoneal reflection and in this setting the incidence of suture line recurrence approaches 25% of all recurrences.

Various techniques which have been shown in animal and in limited human studies to be effective in preventing suture line recurrence have been reviewed. Perhaps the most effective surgical principles to be used in preventing this complication are wide local excision and intraluminal-intraoperative irrigation of the bowel with a cytotoxic agent.

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# Traumatic Rupture of the Thoracic Aorta

SAUL KATZ, M.D.

The thoracic aorta is ruptured in ten to seventeen percent of all traffic deaths.<sup>1,2</sup> In 1975 there were 203 vehicular deaths in Maine and 46,000 in the United States.<sup>3,4</sup> Since eighty to ninety percent of those with ruptured aorta are dead at the scene of the accident we can expect each year in Maine that two to seven people will be alive with ruptured aorta following the initial trauma.<sup>2,5,6</sup>

Of those alive one-half hour after the injury but untreated, thirty percent will be dead at six hours and forty-nine percent at twenty-four hours. This threat to life continues beyond the immediate post-traumatic period. Seventy-two percent are dead at

eight days and ninety percent will have died by four months.

## MECHANISM

The principle mechanism of rupture is thought to be a difference in deceleration between the mobile aortic arch and fixed descending aorta.<sup>7</sup> At the moment of impact the aortic wall is flexed, stressed, and disrupted at the juncture of these two segments just beyond the origin of the left subclavian artery. The tear occurs in the intima and media and can be partial or completely circumferential. The torn ends retract leaving the adventitia and mediastinal pleura to contain the hematoma and prevent exsanguination. It is the integrity of this thin tissue layer that determines whether or not the patient survives long enough for surgical intervention. The resulting hematoma may dissect the aortic wall and cause compression of the true lumen, resulting in the

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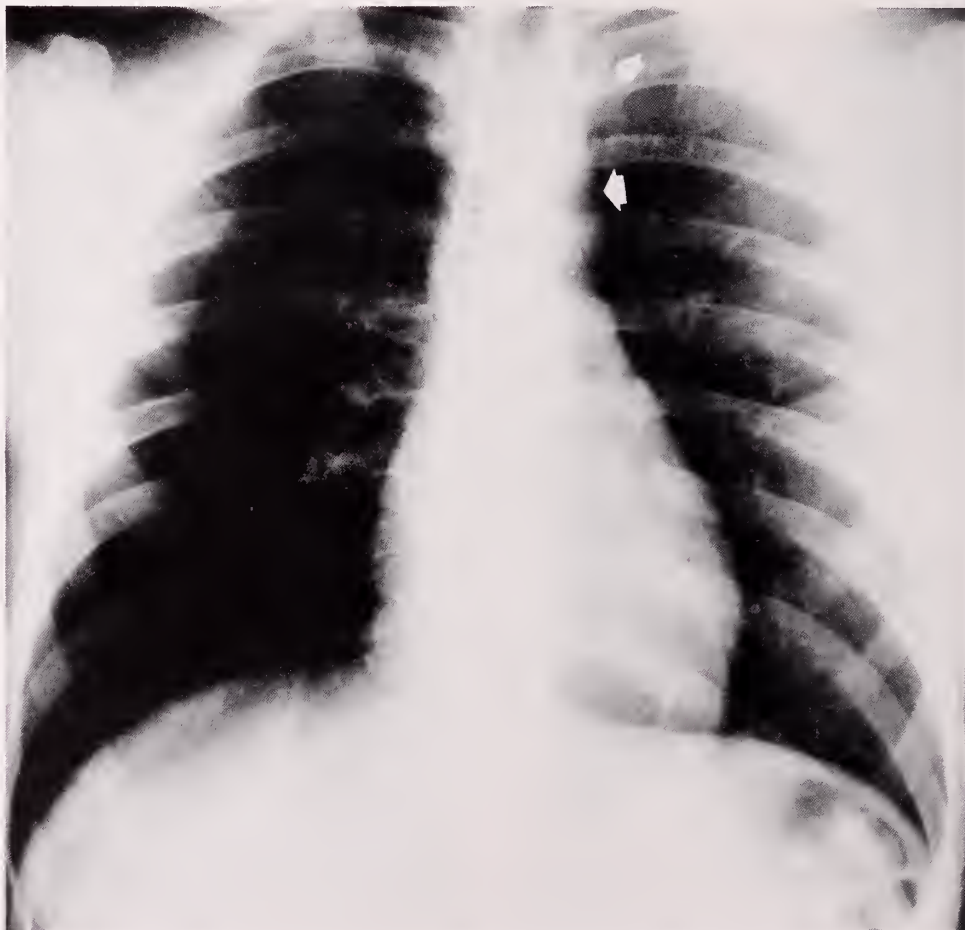


Fig. 1. The PA chest film shows fracture of the left first rib, distortion of the aortic knob (lower arrow) and obliteration of the medial aspect of the left upper lobe (upper arrow) without widened mediastinum.



Fig. 2. An AP chest x-ray demonstrates widening of the mediastinum, blurring of the aortic outline and opacification of the clear space between pulmonary artery and aorta.

“acute coarctation” syndrome of upper extremity hypertension and a systolic murmur.<sup>8</sup>

The forces involved in producing an aortic tear frequently result in multiple associated injuries to the skull, long bones, and abdomen.<sup>2,9</sup> Contusions of the heart and lungs are common, and can complicate postoperative management.

#### DIAGNOSIS

Traumatic disruption of the aorta should be suspected in multiple trauma patients, particularly those subjected to sudden deceleration injury such as the driver or front seat passenger in a head-on automobile collision. The external signs of trauma may be no more than bruises and ecchymosis; indeed there may be *no* visible clues to the severity of the injury.<sup>2,8</sup> Upper extremity hypertension or a difference in pulse pressure between the arm and leg or between the two arms is an important finding but is present only about one-third of the time.<sup>11</sup> Similarly, a systolic murmur heard over the back and precordium is evidence of an aortic tear but is found in only twenty-six percent of patients.<sup>11</sup>

A plain chest film will suggest aortic injury in most

but not all of these patients (Figs. 1,2). A vertebral or first rib fracture indicates that trauma has occurred that may have been severe enough to damage the aorta. Widening of the mediastinal shadow to eight centimeters or more on the one-hundred centimeter AP supine film is indicative of bleeding into the soft tissues, as is blurring of the aortic knob or descending aorta, blunting of the angle between aorta and pulmonary artery, or obliteration of the medial portion of the apex of the left lung by extrapleural hematoma.<sup>12</sup> There may be a shift to the right of the trachea, or depression of the left main stem bronchus. In essence, any change in the chest film which interferes with appreciation of all normally visualized contours and structures in the mediastinum may indicate mediastinal hemorrhage. These x-ray findings are helpful when present but their absence does not ensure integrity of the thoracic aorta, as the chest film may be normal despite an aortic tear.<sup>10</sup>

*Suspicion of aortic injury mandates an aortogram, for it is the only study whereby traumatic aortic rupture may be confirmed or disproved.* It provides accurate information as to the location and

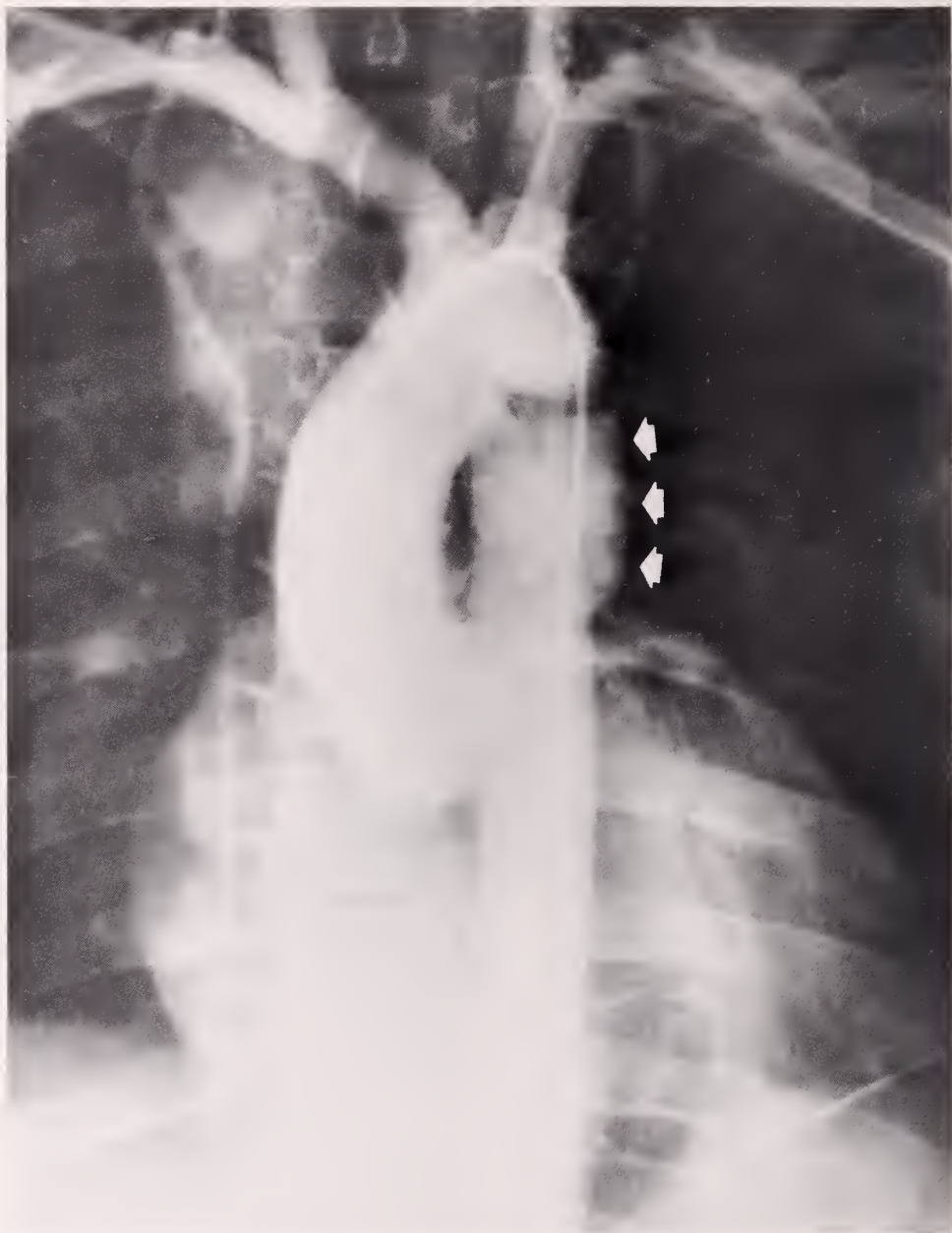


Fig. 3. The aortogram demonstrates disruption and separation of intima and media and compression of lumen by dissecting hematoma (arrows).

extent of the damage. The study may be performed retrograde through the right brachial artery or through the femoral artery. The latter approach has become standard in recent years as angiographers have gained confidence in directing the catheter past the aortic tear. The angiographic features of aortic tear may be limited to a transverse line of decreased density of contrast medium or may show extensive disruption, extraluminal extravasation, and narrowing of the true lumen (Fig. 3).

#### TREATMENT

Surgical therapy consists of placement of a tube graft to reunite the torn and retracted ends of the

aorta. The approach is through an elongated left posterolateral thoracic incision. Principles of management include determined avoidance of the hematoma as it is very tenuously contained and disruption may lead to rapid exsanguination. The aorta must be freed proximal and distal to the hematoma to permit encirclement by tapes and later placement of the cross clamps. A double lumen endotracheal tube permits ventilation of the right lung and collapse of the left lung for adequate exposure. This also helps to avoid intrapulmonary hemorrhage on the left due to a combination of prior injury, operative manipulation, and heparinization.

Although there are reports of successful repair



Fig. 4. A saccular aneurysm in a patient who presented twenty-five years after an auto accident with bronchial erosion and hemoptysis.

without provision for distal circulation, most surgeons prefer to maintain perfusion to the lower half of the body during aortic cross clamping.<sup>9,11,13</sup> In addition to providing blood flow to the spinal cord through its lower thoracic and lumbar supply, bypass decreases the volume of blood flowing through the left ventricle and avoids upper extremity and cerebral hypertension, left ventricular decompensation, and pulmonary edema. Bypass technique allows suctioning of lost blood and its return to the circulation. It is usually conducted from left atrium to left femoral artery or left femoral vein to left femoral artery.

An additional method of providing distal blood flow and decompression of the proximal circulation is the use of a temporary shunt.<sup>14</sup> The Gott shunt is a polyvinyl tube with a nonthrombogenic heparin bonded inner surface that may be placed from the left subclavian artery, ascending aorta, or the apex of the left ventricle to the distal thoracic aorta or femoral artery.<sup>15</sup> Its use avoids the need for heparinization as may be particularly desirable in the patient with multiple injuries.

Repair of the aorta should be the initial procedure

in the patient with multiple injuries because of the continuing threat of rupture of the hematoma and exsanguination.<sup>2</sup> The aortic injury takes precedence over all other considerations except for progressive intracranial hemorrhage or severe continuing intraabdominal bleeding.

#### MAINE MEDICAL CENTER EXPERIENCE

Fourteen patients with nonpenetrating aortic injury have been seen in the past five years.\* Twelve were males, a predominance noted in most reports.<sup>9,16</sup> Eight were involved in automobile accidents and six had been riding motorcycles.

Eight patients were seen within the acute phase. They were eighteen to thirty-five years old and all had sustained additional injuries. Hypertension or a differential blood pressure between upper and lower extremities was noted in seven of the eight, and a murmur was heard in three. Their condition on admission varied from that of an ambulatory eighteen

\*The author wishes to thank Doctors Clement Hiebert, Chris Lutes, Jeremy Morton, Edward Nowicki, and Richard White for permission to include their patients.



Fig. 5. The retrograde aortogram demonstrates a chronic aneurysm in a patient who presented with a murmur eleven years after a motorcycle accident.

year old man with upper extremity hypertension and subtle plain film changes eleven days after an automobile accident (Fig. 1), to that of a twenty year old man brought to the emergency room in coma and shock. Following resuscitation and an aortogram he underwent repair of his aorta, followed by splenectomy, closed reduction of the right hip, debridement and closure of open right tibial and fibular fractures, skin grafting, fixation of left tibial fractures, and replacement of the right testicle and repair of the scrotum. He had also sustained multiple fractures of the skull, ribs, clavicle, and pelvis as well as cerebral and cardiac contusions. The patient was dis-

charged well three months later.

Seven of the eight patients underwent operation and survived. The eighth patient expired after the aortogram but before surgery could be initiated.

Six patients have been seen with chronic aneurysms from three to twenty-five years after injury. Surgery was performed in five because of the continuing danger of expansion and rupture of the aneurysm. Four survived. The aneurysms ranged from four to twelve centimeters in diameter and most had some calcification within the wall (Figs. 4,5).

One fifty-two year old man was transferred fol-

lowing a motorcycle accident with a widened mediastinum and fractures of the first through seventh ribs. An aortogram was positive. At emergency surgery, he was found to have a chronic aneurysm without fresh hematoma. This was repaired. Later questioning revealed that he had injured his chest in a jeep accident ten years earlier.

#### CONCLUSION

Traumatic aortic rupture should be suspected from the nature of the injuring mechanism and the trauma sustained. Its presence should be suspected in patients with multiple trauma, closed chest injury, clinical evidence of acute coarctation, or plain film evidence of mediastinal bleeding. The possibility should be considered in any patient who has sustained deceleration injury the force of which may have been severe enough to tear the aorta, with or without clinical or x-ray evidence of aortic trauma. This injury usually occurs in young healthy adults in the midst of their productive years. The possibility of an aortic tear must be routinely entertained; when aortography confirms the diagnosis operation may avert an otherwise lethal outcome.

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# Non-Operative Percutaneous Removal of Retained Bile Duct Stones

## Review of a Two-Year Experience

ANDREW B. PACKARD, M.D. and ROBERT E. MCAFEE, M.D.

### ABSTRACT

Since April 1975, retained bile duct stones have been removed successfully from 9 of 10 patients using the T-tube tract. The 90% success rate compares favorably with a recent review of the national experience from 38 institutions doing the procedure.<sup>1</sup>

Our experience indicates the importance of lateral T-tube placement at the time of surgery.

There have been no serious complications.

### INTRODUCTION

It has been estimated that currently in the United States about 5% of patients requiring common duct exploration during the course of gallbladder surgery require a second operation for retained bile duct stones.

Over the past five years, non-operative techniques have been developed using image intensification fluoroscopy for the percutaneous removal of such retained stones.

The development of this procedure is largely the result of work of H. Joachim Berhenne who has refined the earlier work of Mondet, Mazzariello and Magarety.

The development of these techniques has been fully described elsewhere.<sup>2</sup>

### MATERIALS AND METHODS

A waiting period of six weeks following primary bile duct surgery has been customary to allow the T-tube sinus tract to mature.

Patients are premedicated with a broad spectrum antibiotic beginning twelve hours prior to the procedure and for 24 hours afterward.

Demerol® and Atropine® are given routinely just prior to the procedure.

A cholangiogram is done through the indwelling T-tube to confirm and localize the retained stones. The T-tube is then removed.

A commercially available steerable catheter\* is introduced through the sinus tract and retained stone or stones are approached.

Following the passage of a steerable catheter to, or preferably beyond the stone, a DORMIA\* wire ureteral basket sheathed with a small plastic catheter is passed through the large catheter to a point opposite or beyond the stone.

The large catheter is then withdrawn, the basket is



opened and an attempt to engage the stone is made. If the stone is caught, the basket is closed and the entire apparatus is withdrawn through the sinus tract.

Modifications of the procedure include crushing of soft large stones, suction to engage small fragments, and pushing fragments into the duodenum with the catheter.

A red rubber catheter is left in the bile duct following the manipulation. Patients are hospitalized for a period of twelve hours following the procedure. A repeat cholangiogram is done prior to final removal of the indwelling catheter.

Four patients have required more than one ses-

\*Medi-Tech, Watertown, Massachusetts.

Patient 2



Patient 3

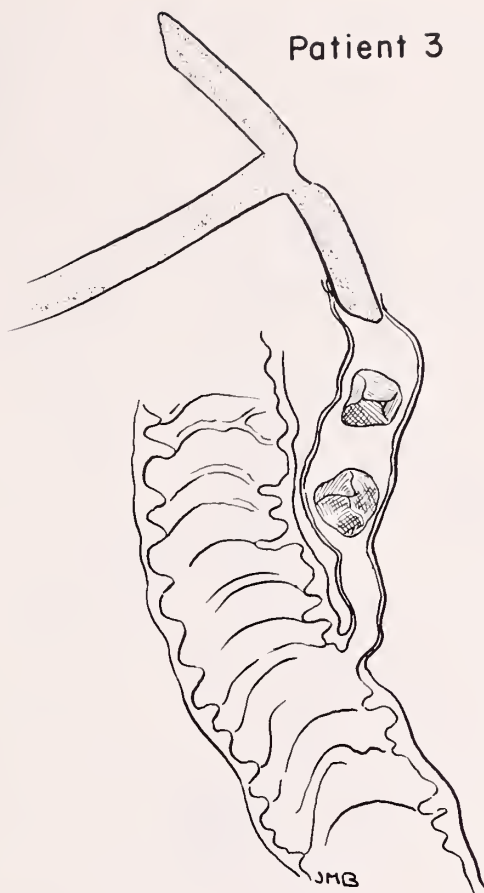


TABLE 1

## SUMMARY OF RESULTS

No.	Patient	Referral Area & Date of Removal	Sex	Age	Size & No. of Stones	Location	Results
1	D.P.	Northern Me. 4-17-75	F	39	9 mm.	Common Duct	Removed 2 session Presented as emergency with tube out.
2	S.N.	Portland 5-14-75	F	19	12 mm.	L. Hepatic Duct	Removed
3	A.M.	Southern Me. 9-12-75	F	38	*11 mm. *13 mm.	Both in Common Duct	Removed
4	R.B.	Portland 2-13-76	F	56	14 mm.	Impacted distal Common Duct	Removed. 2 sessions required
5	L.T.	Portland 8-25-76	F	74	10 mm.	Common Duct	Stone fragmented. Fragments pushed into duodenum. 2 sessions.
6	M.B.	Mid-Maine 10-8-76	F	31	8 mm.	Common Duct	Removed
7	H.W.	Mid-Maine 10-24-76	F	68	4 mm. 5 mm.	Both in left Hepatic Duct	Removed
8.	D.S.	Portland 11-22-76	F	43	15 mm.	Common Duct	Removed
9.	L.R.	Portland 1-24-77	M	67	9 mm.	Common Duct	Stone Removed. Half fragment removed. Other small fragments pushed into duodenum.
10.	N.C.	Northern Me. 2-28-76	F	33	9 mm. 10 mm. 13 mm.	L. Hepatic Duct	Unsuccessful.

sion for complete removal. In these cases the antibiotic is continued and the analgesia is readministered.

#### RESULTS (SEE TABLE 1) CASE 1

Presented as an emergency about 12 hours after having inadvertently removed her T-tube at home. A red rubber catheter

was inserted with some difficulty. A second session was required for successful removal of the stone.

#### CASE 4

Presented with a firmly impacted distal common duct stone. The stone could not be dislodged the first day but the manipulation fragmented the stone enough so that fragments could be removed at the second session. An interval of one week passed

## Patient 5



common bile duct could be entered through the very tortuous sinus tract, the bend in the tract caused poor control of the end of the catheter and it was impossible to pass any instruments, including a small arterial guidewire past the three left hepatic duct stones.

### CASES 2, 3 AND 6

All had single stones which were removed fairly easily in one session.

### DISCUSSION

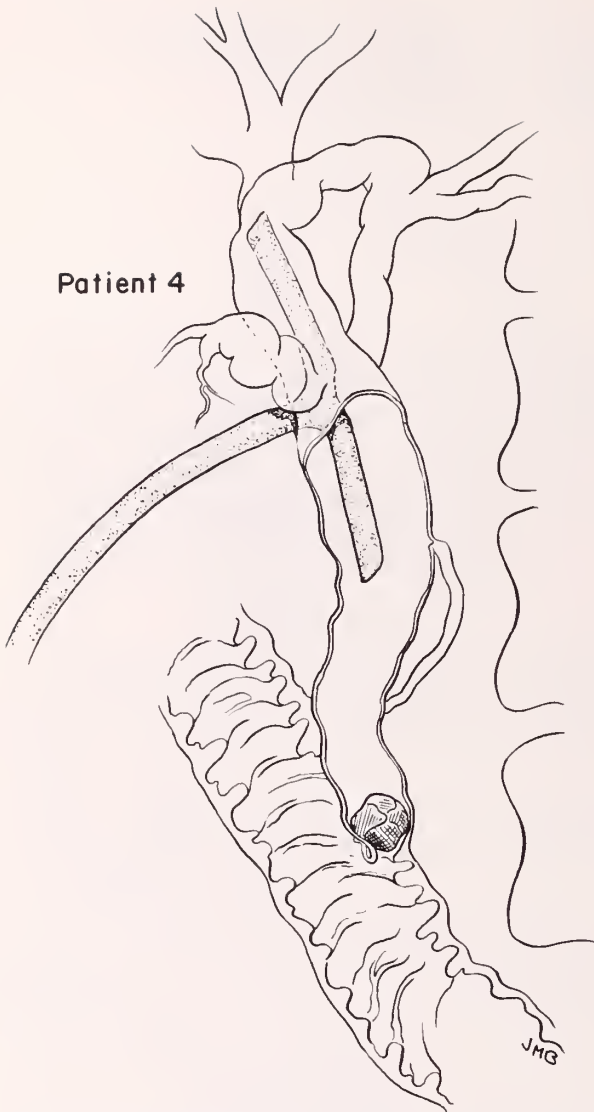
Despite reports of a low incidence of serious complications and morbidity, and no reported mortality in 612 patients undergoing this procedure, we continue to regard percutaneous bile duct stone removal as a procedure carrying potential serious hazard.

Reported complications have included sinus tract perforation, subhepatic bile collection, septicemia (2%), pancreatitis, significant vasovagal reactions and emergency re-operation for failure of stone extraction.

Bile duct perforation, although not reported, is a continuing very serious potential hazard. Because of these potential situations, particularly these requiring emergency surgery, and also because of our referral pattern with some patients coming from a distance, we have resisted doing the procedure on an outpatient basis. Perhaps, with more experience, this policy will be modified in selected patients.

Some patients do complain of dull pain during the manipulation as well as exhibiting vagal symptoms so that we think pre-medication with Demerol and Atropine is in order.

## Patient 4



between the two sessions with the tip of a red rubber catheter lying against the stone.

### CASE 5

Patient had a stone that was difficult to visualize fluoroscopically. Two sessions were required to fragment the stone and push the fragments into the duodenum.

### CASE 7

A second session was required to remove a small fragment seen on post-procedure cholangiogram.

### CASE 8

Involved the removal of the largest stone in the series. This calculus had to be forcefully extracted through the sinus tract and a small perforation of the external end of the sinus tract resulted. A tube could not be re-inserted following the stone removal but the patient remained asymptomatic.

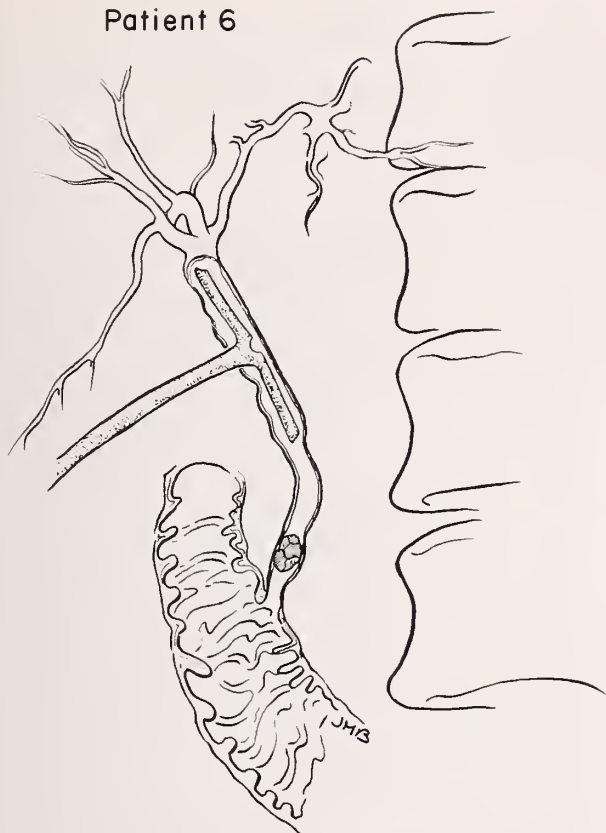
### CASE 9

The common duct stone was fragmented. A larger fragment was removed and the smaller remaining pieces were pushed into the duodenum in three passes.

### CASE 10

This patient's tube was medially placed through the cholecystectomy incision causing an unfavorable approach. Although the

Patient 6



Patient 7



Patient 8



One episode of fever following manipulation has also engendered the routine use of prophylactic broad spectrum antibiotics.

We consider ourselves fortunate both in our success rate and also the lack of any major complication. The one case of sinus tract perforation (case #8) was self limited and the patient had no symptoms. The importance in allowing six weeks following surgery for maturation of the sinus tract before instrumentation is essential to minimize the risk of perforation.

The importance of positioning the T-tube at the time of surgery through either a lateral stab wound in the case of a vertical incision or at the lateral end of a subcostal incision seems imperative to facilitate a technically easier and safer procedure. We feel that our failure in case #10 was, in part, related to a medial tube placement with resultant sharp angulation (see illustration).

The desirability of a large T-tube, that is, #14 French or longer, has been previously emphasized. If a small T-tube is necessary, an outer sleeve of larger diameter as the tube courses the abdominal wall can be utilized to create a wider sinus tract.

Our experience to date indicates that in most cases of retained bile duct stones, an attempt at percutaneous removal is worthwhile.

A retained stone was fragmented and removed from the left hepatic duct of an eleventh patient on August 9, 1977.

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Patient 9



Patient 10



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#### ACKNOWLEDGEMENT

The authors are grateful to Judith Barrington for the excellent illustrations of the 10 patients.

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## Fall Meeting of the M.M.A. House of Delegates

Saturday, December 10, 1977

Waterville, Maine

12:30 P.M. — Registration; 1:00 P.M. — Lunch; 2:00 P.M. — Meeting

10:00 A.M. — Meeting of the Executive Committee

# The Medical School of Maine at Bowdoin College (1820-1921)

AVANELLE P. MORGAN, M.D.

## GENERAL SURVEY OF MEDICAL EDUCATION IN THE UNITED STATES

The first medical school in the U.S.A. was established at the College of Philadelphia in 1765. Previously, all physicians were either trained as apprentices or students at a university in Europe. The first school was designed to follow in the Edinburgh tradition. There were five areas of study: anatomy, materia medica, botany, chemistry, and the theory and practice of medicine. Surgery, as such, did not appear. Hospital training also was not included.

"Before the Revolution, the class of 'regular' physicians had attracted those who wished to be called 'urbane or English or fashionable' rather than those who genuinely believed that they were to offer better treatment. In the years following the Revolution, there remained a widespread willingness to use the services of orthodox doctors instead of cultists and quacks."<sup>1</sup> The Revolution demonstrated the necessity for surgeons whose knowledge was often tested by their commanders. This made examinations a familiar fact and also contributed to the development of licensing procedures after the war.

Medical societies were organized on a statewide basis. Massachusetts Medical Society was founded in 1781. These organizations tried to regulate professional standards. The medical school soon developed and became another basis of regulation. This was difficult to coordinate in regulatory bodies, in that physicians generally practiced from their homes, with little or no contact with other physicians.

The opening of a rash of independent medical colleges at the beginning of the nineteenth century created a new problem. "There could not be a standardized profession unless there was a standardized educational system; quality control thus became a real issue. In 1800 there were only 4 functioning medical colleges; in 1825 there were 18. Between 1810 and 1840 26 new medical schools were founded; between 1840 and 1876, 47; and in the great wave of immigration (1873-1890) 114 new schools were established. Altogether, it has been estimated, over 400 medical schools were founded between 1800 and 1900."<sup>2</sup> The medical schools developed between 1800 and 1825 were generally established with liberal arts colleges. However, university medical schools were outnumbered by proprietary schools. The former had difficulty maintaining students while in competition with the latter. They did maintain contact with the latest medical developments in Europe. With the beginning of western migration medicine became insular.

The issue of medical regulation was confused in the 1830's and 1840's by the establishment of licensing regulations. Also state regulation of medical societies was withdrawn. Maine, among others, lifted all restrictions on unlicensed practitioners. By 1845 eight states had no guidelines by which the populace could evaluate medical standards. Physicians were "not entirely unhappy with the demise of licensing." Many of the existing licensing laws were ineffective and confusing, and in some cases they were being used for those restrictive activities which were solely for the benefit of sections of the profession. The country was largely rural; the medical societies largely centered in the towns. In the latter professionalism developed with enormous speed. By the 1830's there was also a network of medical societies concerned more with fighting quackery than with raising their own standards.<sup>3</sup>

New medical societies developed in the 1840's. This was a means by which regular and irregular physicians could be separated without fear of being sued. The American Medical Association (AMA) was founded in 1847. In the 1850's AMA membership was proposed as a means of certifying practitioners based on competence. However, internal unity and strength were not developed until 1902. The influence of a national organization led to the organization or reorganization of local and state medical societies. Besides this, medical journals flourished in the mid-nineteenth century.

The 1860's revealed a physician more realistic about the future needs to provide more well-trained physicians. Also, means to regulate doctors were developed. The method of teaching by clinical experience was introduced. Pharmacy also became an independent profession. Hospitals for eye and ear diseases, mental illness and other specialties were organized. Although specialist interests were evolving, there were virtually no full time medical specialists in the 1860's. "The American physician was still a general practitioner-physician, surgeon, and midwife."<sup>4</sup>

The state legislature, under the Medical Practice Acts, became the controller of medical licensure in the 1870's. Medical schools were standardized only after licensing was in effect.

With increased immigration and urbanization the hospitals were developed. The institutionalization of medicine began in the latter half of the nineteenth century. The city practitioners became the organizers of the profession. Black physicians began a national organization as well as medical schools in the 1870's-1890's.

The goal of educational institutions and medical societies was directed toward upgrading the standards of entry into the profession rather than creating an educational elite. The numbers of practitioners would decrease by necessity. But with the advances in technology, the dawn of specialization was near. Also, the European medical schools, particularly in Germany, attracted many American students in the 1870's-1890's. The teachers of students began to question whether or not different curricula should be used to train different "types" of physicians. This was resolved with the abolition of the "track" system. Affiliation with hospitals also became a necessity in the late nineteenth century.

Twenty-two of the more progressive medical schools established the American Association of Medical Colleges (AAMC) in 1876. Registration of colleges began in 1879-1880. Many members left when the AAMC required three courses of lectures instead of two. With the organization of state examining boards, teaching would be separated from licensure. Also, this could and would be used as leverage against the schools for reform.

The period from 1890-1914 can be referred to as the era of reform. The common goals of medical societies, licensure associations, and many colleges were: "the upgrading of entrance standards to the profession, the specification of curricula in the medical schools, the suspension of the weakest proprietary institutions, and the reduction of the number of students graduating from medical schools."<sup>5</sup>

The AMA published its journal with articles in the early twentieth century exposing the unequal standards of education. Affiliations with state societies followed. In 1904 the AMA Council on Medical Education was formed. This acted as a source of information for the AMA and agent to carry out recommendations. Its ideal standards included: "preliminary education at the university level; five-year medical course (one year of physics, chemistry, biology, two years of the laboratory sciences, two years in the clinical branches); and a sixth year as an intern."<sup>6</sup> Minimum standards were "four years high school for admission; a four-year medical course; and satisfactory licensing examination."<sup>7</sup> In 1906 schools were classified A (acceptable, B (doubtful), and C (unacceptable).

The Carnegie Foundation for the Advancement of Teaching was organized in 1906. Law, theology, and medicine were to be investigated by the division which was directed toward problems in higher education. They joined forces with AMA Council on Education in 1908. The investigation was concluded in 1910 with the publication of the Flexner Report. Of all schools only Harvard, Johns Hopkins, and Western Reserve received a "clean bill of health." The primary force for improvement was to be a large permanent endowment. Also stressed was the university form of education system, therefore excluding the proprietary schools. Between 1904 and 1915,

ninety-two schools either merged or closed their doors. By 1920 only eighty-five remained. The Carnegie Foundation offered subsidies to the better schools to make the necessary improvements. The report discriminated against the black student and the financially poor student. By its very nature, the report caused schools to be maintained in relatively large urban areas. Fragmentation of health care into specialized areas was on the horizon.

#### ORIGIN OF THE MEDICAL SCHOOL OF MAINE

Bowdoin College was established in 1794 at Brunswick, Maine. The charter was granted by the General Court of Massachusetts. Rev. Joseph McKeen was inaugurated as president in September of 1802. The school was opened the following day. The first class graduated in 1806, receiving bachelor of arts degrees.

Throughout the initial twenty-five years, the liberal arts college grew. Early benefactors, such as Hon. James Bowdoin bequeathed funds and land for the college.

During the administration of the third president, Rev. William Allen (1819-1839), the state of Maine separated from Massachusetts and was admitted to the Union. The first Legislature of Maine passed the following law in 1820:

Section I — "Be it enacted by the Senate and the House of Representatives, in the Legislature assembled, that there be and is hereby established under the control, superintendence, and the direction of the President, Trustees, and Overseers of Bowdoin College, a Medical School for the instruction of students in Medicine, Anatomy, Surgery, Chemistry, Minerology and Botany.

Section II — Be it further enacted that the President, Trustees, and Overseers of Bowdoin College be, and hereby are authorized to appoint, and it shall be their duty to appoint, as soon as may be, learned professors of Medicine, Anatomy, Surgery, Chemistry, Minerology, and Botany, who shall deliver regular lectures in their respective branches at such time as the corporation shall prescribe.

Section III — Be it further enacted that there be and hereby is granted to the President, Trustees, and Overseers of Bowdoin College for the benefit of said Medical School, and for the procuring of necessary books, plates, preparations, and apparatus, the sum of \$1,500.00 to be paid out of the Treasury of the State, out of any monies not otherwise appropriated by law, and the further sum of \$1,000.00 annually until the legislature orders and directs."

President Allen contacted Dr. Nathan Smith regarding the proposed medical school. Dr. Smith was at that time Professor of Medicine at Yale University. He had founded Dartmouth School of Medicine. Dr. Smith's reply to President Allen was:

I think after what experience I have had, we could form a medical school that would, in point of real utility, equal any in this country. In a new state like Maine, where neither habit nor parties have laid their ruthless hands on public institutions, and where the minds of men are free from their poison-

ing influence, everything is to be hoped for. Such a field as would be very inviting to me, and such a place I take Maine to be. For though they have heretofore been divided into parties, I am disposed to think they have become a state unto themselves, party spirit will in great measure subside and they will be ambitious to promote honor and the welfare of the state.<sup>9</sup>

Thus the foundations of the eleventh medical school of the United States was established.

In the spring of 1821, twenty-one men entered the first class of the Medical School of Maine. At that time there were only three members of the faculty: Nathan Smith (Theory and Practice of Physic and Surgery), John Doane Wells, also a Harvard graduate, (Anatomy and Physiology), and Parker Cleaveland (Chemistry and Materia Medica). Similar to other American Schools there were few entrance requirements and teaching was almost exclusively done by lecturing. Massachusetts Hall was the only building designated for use by the Medical School.

### THE FIRST FIFTY YEARS

The lack of standardization of medical school requirements is discussed by Dr. James Thatcher (1821) in the following:

Although there is no uniform standard of attainments established, in order to graduation, in most of our schools it is required, that before a student can be admitted to an examination for a degree, he must have attained the age of twenty-one, have studied three years with some regular physician, attained two full courses of lectures on the different branches of medicine, and, if he has not enjoyed the advantages of a collegiate education, he must furnish satisfactory evidence of having made respectable classical attainments; and particularly that he has acquired a competent knowledge of the Greek and Latin languages, has studied mathematics, natural and experimental philosophy, geography, and belles lettres. In several of our new schools it is required that he shall have attended the clinical practice of some infirmary for a specified term. It is also required that, before he can receive his degree, he must pass a close examination in the different branches of medicine, and write and defend a thesis on some medical subject.<sup>10</sup>

Multiple additions to the curriculum were made in the succeeding years. A course in obstetrics was begun in 1825. The department of Materia Medica and Therapeutics was formed in 1846. In 1849 Medical Jurisprudence was added. This was followed in 1857 by the Department of Anatomy and Physiology. Public Hygiene was last in 1872.

The annuity supplied by the State Treasury only continued until 1834. At this time the Medical College of Maine surpassed all other New England schools in the areas of medical libraries and apparatus. The fund for the college however were practically limited only to the tuition of the students. These were paid directly to the professors. While graduates of Bowdoin College contributed to general funds and endowments, this was not necessarily true for the graduates of the Medical College of Maine. In 1858 the Medical College formed a petition for a building fund, which failed. The State Legislature would grant the petition only if they could "make any necessary regulation for the admission and graduation of students."<sup>11</sup> This ruling

was accepted and Adams Hall was opened in 1862. However, because this was distasteful to the Maine Medical Association, all Bowdoin graduates were refused membership. This ruling was repealed in 1864.

### THE SECOND FIFTY YEARS

The need for a hospital for surgical patients and for the insane was brought to the foreground several times, but limitation of funds negated the proposal. However, laboratory courses were finally added to the curriculum in 1875. This change was accompanied by lengthening the semesters from twelve to twenty weeks. The tuition was also increased to \$83.00 plus a \$25.00 fee for graduation. If the student did not have a college degree he was required to take an entrance examination. Previously no prerequisites were required other than tuition.

The 1880s again heard the request for increased clinical exposure. It was proposed to move the Medical School of Maine to Portland. The first endowment was contributed by Mrs. Catherine M. Garcelon, in memory of her husband and brother (both graduates of the medical college at Bowdoin) for the purpose of building a hospital at Brunswick.<sup>12</sup> However, endowments for the medical school were sporadic.

Through the first seventy years the medical school existed as a separate entity on the Bowdoin campus. President Hyde in 1897 stated that "the present connection between the Governing Board and the Medical School is little more than nominal, and the mode of administering its affairs is primitive in the extreme. The existing methods and relations are those which tradition has handed down, when such methods and relations prevailed in professional schools throughout the country. The prospect of a considerable endowment in the future and the increasing need of materials for the study of medicine indicate that the time has come for placing the Medical School in closer relations with the Governing Boards, and administering its finances in a more impersonal method."<sup>13</sup> Previously the professors had divided the fees and arbitrarily divided the funds. From 1897 on, the Governing Boards were to pay the salaries and appropriate funds.

The controversy as whether or not to move the Medical School to Portland was again raised in the 1890's. President Hyde listed five points against moving the School. They were:

1. The facilities are established, *i.e.*, a lecture hall, museum, library, and dissecting room.
2. The laboratories for chemistry, bacteriology, and histology are "perfect".
3. The intimate association with the college maintains its liberal attitudes and avoids commercialism.
4. There is a traditional association between the Medical School of Maine and Bowdoin College and none particularly with a city.
5. It is less expensive to live in Brunswick.

The majority of the faculty favored the move to Portland. Their reasons were:

1. The Medical School could be connected with the Maine General Hospital for clinical purposes. The hospital's charter included educational purposes as part of its function.
2. There would be increased variety and quantity in clinical experience.
3. Provisional arrangements for securing a lot near the hospital had been made.
4. Most professors lived in Portland. With the increased length of the school year, they could add more lectureships more conveniently.
5. Across the nation, city schools were increasing secondary to the number of classes and producing the highest grade of medical talent.

By 1899 the transfer of the two clinical years was completed. The Medical School building, located on Chadwick Street, was rented part of the time by the Portland School of Medical Instruction. The Medical School assumed the mortgage of their building. They planned to move the entire school to Portland provided they could build a second building. A dispensary was erected for the care of the poor.

Dean Addison Thayer stated that "excepting the temporarily useful Portland School for Medical Instruction and the worse-than-useless Druidic University (in Lewiston) and its dubious appanage, our school is the only medical school in Maine. . . . Almost to the beginning of the present century (the twentieth) all American schools of medicine were commercial. To escape the stigma, university affiliations have been made or strengthened. . . . It is only in recent years that material inheritances and benefactions have come to schools of medicine. Commercial schools of medicine, of the type which is now disappearing, neither deserved or received benefit."<sup>14</sup>

With the turn of the century, great progress was being made. In 1904 the four-year medical school was established. The requirements for admission were raised to include background in English, Latin, Chemistry, and Physics. The Medical School of Maine was accepted by the American Association of Medical Colleges. The faculty recommended two years of work as a prerequisite. This was mandatory by 1916.

The Carnegie Foundation for the Advancement of Teaching visited the Medical School in October of 1909. This report, better known as the Flexner Report, had a profound and lasting effect upon the school. All aspects of the school were severely criticized. The entrance requirements were considered to be below college standard. Resources for the maintenance of the school only totaled \$15,700. The basic sciences were taught by professors who only lectured occasionally and looked in on laboratory sessions. The responsibility for the laboratory was often delegated to recent graduates. Pharmacology was not taught at all. The clinical facilities were centered around the Maine General Hospital. The

cases were often limited to surgical problems. Teaching was mostly done in the amphitheater based on current cases. According to the report, there was no educational benefit to seeing patients in the dispensary. In spite of these remarks, the school was designated Class A, acceptable.

In reply to the Flexner Report, President Hyde of Bowdoin said, "Maine is not sufficiently populous and wealthy to support a school with equipment and endowment equal to that of Harvard Medical School or the Medical School of Johns Hopkins University, though if schools of that kind are the only schools needed in the country, then the Medical School of Maine, and scores of other Medical Schools, with long and honorable records of usefulness is at an end."<sup>15</sup>

Dean Thayer, of the Medical School, responded by encouraging the faculty to fully evaluate the report and act upon the just criticisms. The Board of Trustees and the Overseers passed the previously mentioned entrance requirements. Dean Thayer also referred to the possibility of changing the four-year school into a two-year basic science medical school similar to the Dartmouth College Medical School. He and other members of the faculty felt that there was sufficient clinical material in Portland to continue as a four-year medical school. Dean Thayer's interpretation of Abraham Flexner's opinions wavered somewhat "but was always decidedly poor."<sup>16</sup>

The Medical School turned to Bowdoin College for financial support, but compared to the amount it needed, it received little. Because of the limited clinical facilities, the school could not increase the number of students in order to obtain additional fees. The alumni were approached but under the shadow of the damning report, the contributions were limited. The State Legislature was asked for an appropriation of \$50,000 annually for two years. The reasons presented to support the school were that primarily the residents of Maine were trained at the Medical School of Maine. It would accept an affiliation with the Department of Public Health and would supply the physicians needed for the small towns. The bill was vetoed by Governor Baxter. In 1920 a second bill was passed to make the Medical School a state institution and move the basic science equipment to Portland. If enacted and the Class A status maintained, Mr. Hugh Chisholm offered to erect a building. This too, was vetoed by Governor Baxter.

In 1918 the Trustees of Bowdoin College voted to close the Medical School in 1921. The Overseers of Bowdoin College vetoed the proposed action. The budget suggested by the Council on Medical Education of the AMA required operating funds of greater than \$25,000 annually. Unless this was maintained, the Class A status would be changed. The Medical School had an annual deficit of \$7,000 as compared to the figure necessary to function at an optimal level. There was no source from which the needed

funds were to be obtained. The trustees voted in 1919 to close the Medical School or have it run independently from Bowdoin College, should no endowment be established to cover the deficit by June, 1921. Should the school close, arrangements would be made to transfer the students, not graduating that year, to other medical schools.

Funds were not obtained and in June, 1921 the Medical College of Maine ceased to exist. President Sills expressed the sentiments of Bowdoin College in the annual report of 1920-1921.

To those who have known the college intimately, the closing of the Medical School naturally brings much regret. The college has had so many points of contact with the medical profession of Maine throughout these hundred years, and has received so much generous and loyal support from the graduates of the Medical School that the abandonment of the School means a very great loss. The loss, however, is as nothing compared with the impairment of reputation, both of the College and of the School, that would have followed inability to maintain the school properly. Furthermore, in these days when economy is so essential and when concentration of resources is so desirable, the College could not afford to go on year after year with a large drain upon its own insufficient funds.<sup>17</sup>

Dean Thayer presented the faculty's feelings in the following statement. "On the twenty-third of next June (1921) unless the unexpected happens, medical education in Maine will cease to exist. The possibility of future revival appears to be small. . . ."<sup>18</sup>

#### SUMMARY

The Medical School of Maine lasted one hundred years. The reason for closing was primarily the inability to raise sufficient funds for the purpose of carrying out recommended reforms. Fifty years later, the State Legislature and the Maine Medical Association, in conjunction with the major colleges of this state, were similarly unsuccessful in raising funds necessary for the reestablishment of the "Medical School of Maine". The dream persists.

#### FOOTNOTES

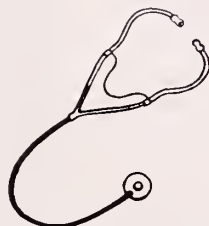
1. Stevens, Rosemary, *American Medicine and Public Health* (New Haven: Yale University Press, 1971), p. 21.
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8. *Charter, Laws, and Regulations of Bowdoin College and Medical School*, Brunswick, 1876, pp. 46-50.
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10. Kahn, Richard, "An Historical Sketch of Medical Education in Maine," *Journal of the Maine Medical Association*, v. 62, pp. 212-213.
11. Hatch, *op. cit.*, p. 464.
12. The Garcelon Fund still exists at Bowdoin College. Pre-medical students are awarded scholarships from it.
13. Hatch, *op. cit.*, pp. 465-466.
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# Anatomy of Maine Medical Center's Emergency Department

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The Maine Medical Center, located in Maine's most populous urban complex, has the largest Emergency Department (ED) in the State of Maine. With seven full-time physicians, a nursing staff of thirty-one, a secretarial staff of seventeen, two physicians' assistants, and the participation of the house staff and medical students, it has also become one of the major departments of the hospital. The volume of patient encounters in the ED increased steadily from 1964 to 1974 (Graph 1). The Department acquired its first full-time physician in 1970 and instituted a triage system the following year so that patients with more urgent or emergency conditions could be seen with dispatch. The increase in the number of patient visits, interestingly enough, occurred during a period when there was a significant rise in the number of physicians establishing practice in the Greater Portland area and while the area's population remained relatively stable.

Many studies of ED visits indicate that other hospitals are experiencing a similar growth in the utilization of emergency facilities as well as an increase in the proportion of non-emergency cases. An analysis of the Maine Medical Center's Emergency Department was initiated to study its changing patterns of utilization and to evaluate medical care. The methodology or results of this study might prove useful to other community hospitals.

## METHODS

Data collection occurred during a two week period in April 1974. All ED visits were documented using a specially designed patient encounter form which recorded patient, arrival, and service characteristics. Additional data were obtained later during a retrospective chart review performed by the Director of the Emergency Department, Dr. Frank H. Lawrence.

The patient population for the two week sample numbered 1,753. Data on the diagnosis, payment source, sex, time, and mode of arrival, date and new or returning status were available for more than 95% (1,662) of the total ED visits.

Upon arrival in the ED, patients are evaluated by

the triage nurse and classed in the following way:

Category I — The Patient's condition is immediately life threatening.

Category II — The Patient's condition is potentially life threatening.

Category III — The Patient's condition is not life threatening, but requires some of the special facilities of an emergency room for proper management.

Category IV — The Patient's requires none of the special features of an emergency room and could be managed properly in any doctor's office.

Data analysis for this study combined Categories I and II as "emergent" (life threatening), with Category III as "urgent" and Category IV as "non-urgent."

## RESULTS

### *Patient Characteristics*

The age distribution presented in Table 1 indicates that nearly three out of four patients were under 45. Young adults were seen most often, followed by those in the 25-44 age group. The sex ratio (Male/Female) of 55.1/44.9, which confirms the data obtained in an earlier study of the ED, is a reversal of the Outpatient Clinic's 34/66 ratio.

A large number of patients being treated during the two week study had previously visited the ED. Repeating patients accounted for 71.5% of all visits. More than half the patients (57.3%) stated they had no family physician. Similar findings were also noted in an earlier ED study.

### *Arrival Characteristics*

Four out of five patients were ambulatory upon arrival in the ED. Almost all the remaining patients (18.1%) arrived by ambulance or rescue vehicle. Only 4.1% were judged emergent; another 35.6% presented urgent conditions. Nonurgent cases constituted 60.4% of the visits.

Slightly more than half the patients (51.8%) were seen during the day shift (8:00 a.m. to 4:00 p.m.). Thirty-seven percent arrived during the evening (4:00 p.m. to 12:00 a.m.) and 10.9% during the night (12:00 a.m. to 8:00 a.m.). Graph 2 represents arrival times during these different periods in 1975.

### *Service Characteristics*

Most patients (71%) required no other services beyond those provided in the ED. Seventeen per-

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GRAPH 1  
MMC ED CENSUS BY YEAR

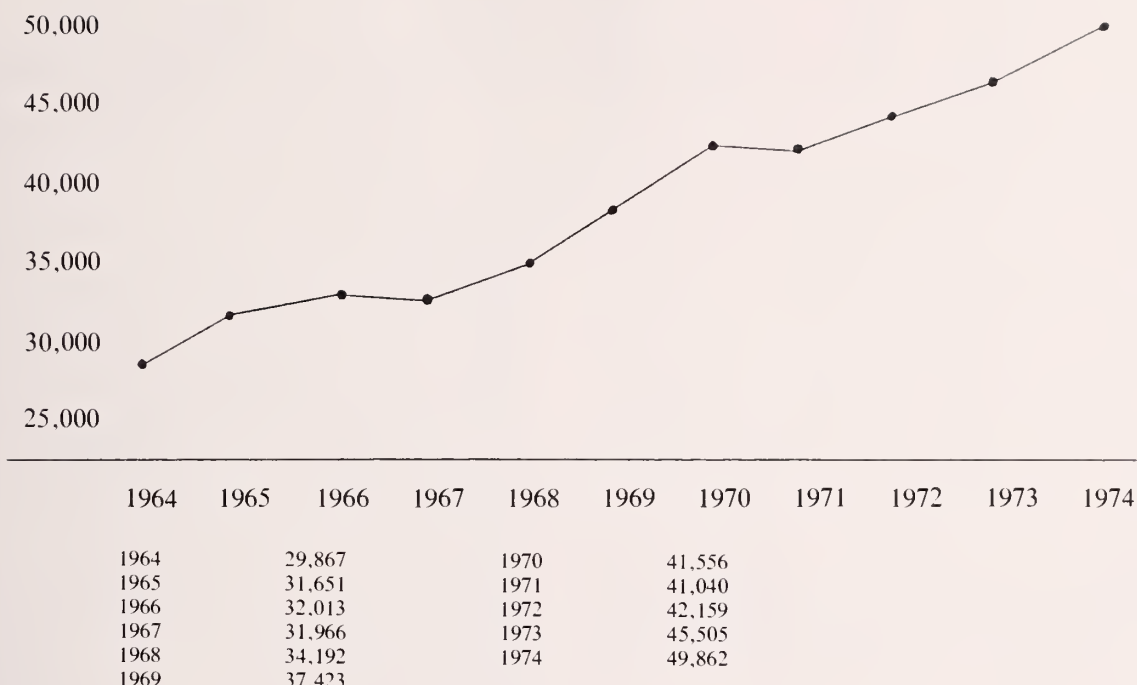


TABLE 1

AGE DISTRIBUTION	
0-14 years	17.7%
15-24 years	31.2%
25-44 years	25.1%
45-64 years	17.7%
65 and over	8.3%

TABLE 2

REFERRAL PATTERNS	
Walked Out	.9%
Return if Necessary	30.1%
Other Agency	2.8%
Mental Health Clinic	2.7%
Other MMC Clinic	27.2%
Private Physician	17.0%
Admit	11.9%
None	4.7%
Other	2.7%

TABLE 3

TEN LEADING IN DIAGNOSTIC CATEGORIES		
	Percent of All Cases	Percent Judged Nonurgent
Lacerations/Burns/Abrasions	22.3%	47.9%
Fractures/Dislocations/Sprains	14.3%	59.4%
Psychiatric	14.0%	58.7%
ENT*	13.9%	82.4%
Abdomen/GI	7.9%	57.9%
Respiratory	6.3%	64.2%
GU/Reprod	6.2%	61.4%
Cardiovascular	5.9%	33.8%
Neurologic	5.0%	50.1%
Other	15.4%	68.9%

\*Includes URI

cent needed x-rays and laboratory tests were performed for 14%. Nearly half the patients were referred to the Outpatient Clinics, other agencies, or a private physician (Table 2). Admission was deemed necessary in 11.9% of the cases. Thirty-five percent were deemed to need no specific follow-up except to return if necessary.

### Comparative Findings

Data on the ten leading diagnostic categories are shown in Table 3. Patients presenting with cardiac problems had the lowest percentage of non-urgent

cases (33.8%) compared with 82.4% of the ENT patients. More than half the patients in each diagnostic group, except for those with lacerations and cardiovascular problems were treated for nonurgent conditions.

Table 4 shows the leading diagnoses by age group. Patients over 45, as expected, were treated most frequently for cardiovascular and respiratory disorders. More than half the cases of lacerations and fractures and 60% of the ENT problems were found in patients under 25. A psychiatric diagnosis was the most common in the 25-44 age group. An analysis of diagnosis by sex revealed some expected differences. Men were more often seen for lacerations, fractures, cardiovascular and respiratory conditions; females for GU, ENT, neurologic and

GRAPH 2  
PATIENT SENSUS BY HOUR OF DAY  
A Three Week Study  
Total Patients = 2,760

Key:  
X March 24-30, 1975  
O August 4-10, 1975  
\* September 22-28, 1975

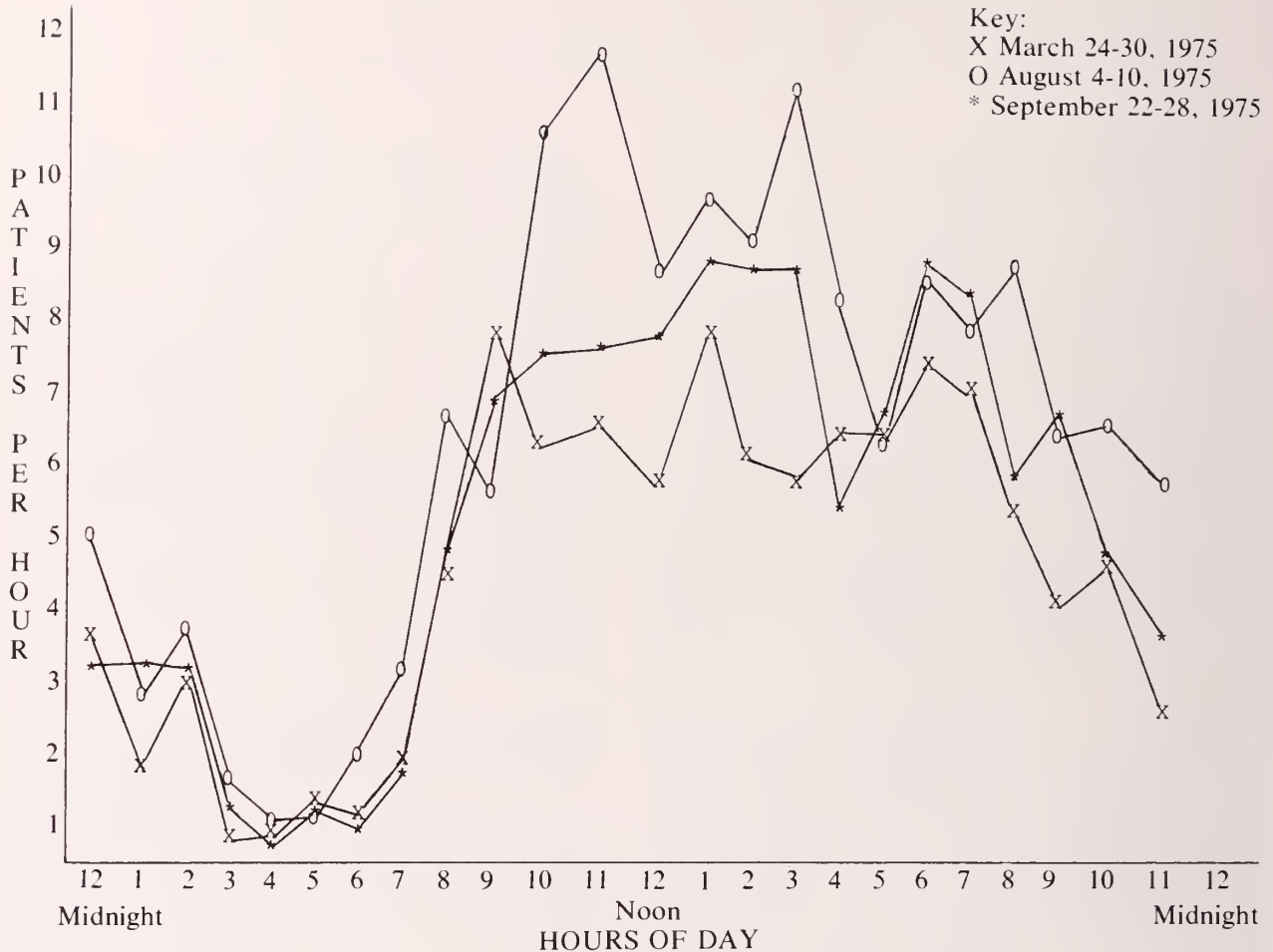


TABLE 4

AGE BY DIAGNOSTIC CATEGORY

Age:		
0-14 years	ENT*, Lacerations, GI, Other	
15-24 years	GU, Fractures, Lacerations, Neurologic	
24-44 years	Psychiatric, GU, Neurologic, GI	
45-64 years	Cardiovascular, Respiratory, Psychiatric, Other	
65 and over	Cardiovascular, Respiratory, Neurologic, GI	

\*Includes URI

psychiatric problems.

Patients with a cardiovascular condition were most likely to have a family doctor. Over two-thirds of the patients with a psychiatric diagnosis reported no family physician.

New patients compiled fewer nonurgent visits, but the difference is not statistically significant. New and repeating patients were also admitted at the same rate. Repeating patients were likely to

come to the ED during the evening or night shifts while most new patients were seen during the day (Table 5).

A comparison of the source of payment show that repeating patients on Medicare or Public Assistance outnumber new patients in these categories by nearly two to one. Nearly half the patients visiting the Emergency Department for the first time were covered by some form of private insurance compared with 38% of the repeating patients.

Table 6 compares the patterns of usage of the Emergency Department population by method of payment. Emergency Department visits by patients on Medicare were most often judged emergent. This group, which presented over one-third of the cardiac problems, also had the highest rate of admission. The Welfare category had the highest rate of nonurgent visits.

### CONCLUSIONS

Data from visits to the Emergency Department of

TABLE 5

COMPARISON OF NEW AND REPEATING PATIENTS						
Shift	Repeating		New		Total	
	Number	%	Number	%	Number	%
8:00 a.m.- 4:00 p.m.	168	13.4	225	50.9	393	22.8*
4:00 p.m.-12:00 a.m.	627	50.0	186	37.1	813	47.2*
12:00 a.m.- 8:00 a.m.	457	36.5	60	12.0	517	30.0*
Total	1252	71.5	471	28.5	1723	100.0

\*p&lt;0.05

TABLE 6

TRIAGE BY METHOD OF PAYMENT				
Payment Source	% of Total	Emergent	Status Urgent	Nonurgent
Medicaid	0.6	0.0	0.4	0.9
Medicare	7.3	30.6	6.1	5.6
Welfare	15.8	6.1	10.7	19.1
Workmen's Comp.	6.7	0.0	10.5	5.9
BC/BS	28.5	26.5	29.8	30.2
Other Private Ins.	13.5	16.3	14.3	10.9
None	12.7	8.2	11.7	14.1
Patient Pays	3.8	0.0	2.2	3.4
Other	11.1	12.1	14.3	9.8

the Maine Medical Center were collected using a patient encounter form. This data was sought to document trends and utilization patterns for decision making about planning for the Emergency Department. Only some of the more pertinent data is presented here.

Most patients encountered in the Emergency Department had nonurgent problems (60.4%). A significant percentage (71.5%) has used the Emergency Department previously and more than half (57.3%) did not identify a family physician. More of the repeating patients were on public assistance or welfare than the first time patients. No specific follow-up was recommended for 35% of the patients.

Armed with this knowledge and knowing the high cost of services rendered the Emergency Department, a special non-emergency unit adjacent to the

Emergency Department was developed. Although the staffing is mixed, the primary provider is a family nurse practitioner with physician support from the Emergency Department.

#### ACKNOWLEDGMENT

The research described in this paper was supported in part by grant No. PHS IR27 MB00002-02 from the Office of Special Programs, Bureau of Health Manpower Education, NIH in cooperation with the Functional Task Analysis Cooperative Study Group. The chief investigator for this grant is Arthur R. Jacobs, M.D., M.P.H., director, Division of Health Care studies at New England Medical Center Hospital and is associate professor, Tufts University School of Medicine. Assistance was provided by Frank A. Hale, Ph.D., and Patricia M. Bennet, Ph.D., both assistant professors in the Department of Community Medicine at Dartmouth Medical School. Of course, the Emergency Department Staff at the Maine Medical Center deserve special thanks.

## Beth Israel Hospital Continuing Education Courses 1978 CONFERENCES

### THE THIRD ANNUAL VAIL FAMILY PRACTICE CONFERENCE

February 11-18, 1978

The Mark, Vail, Colorado

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The Mark, Vail, Colorado

### THE EIGHTH ANNUAL ASPEN RADIOLOGY CONFERENCE

February 25-March 4, 1978

The Aspen Institute for Humanistic Studies, Aspen, Colorado

# Multifocal Glioma Visualized by Contrast Enhanced Computed Tomography

## Report of a Case With Pathologic Correlation\*

L. REED ALTEMUS, M.D. and JOAO RADVANY, M.D.

The *in vivo* visualization of gliomas by contrast enhanced computed tomography (CECT) defines a variety of growth characteristics which previously were revealed only by necropsy study of whole brain sections. How precise these configurations will reflect pathologic changes characteristic of neuroectodermal tumors has yet to be clarified. The practical significance of preoperatively determining the presence of bihemispheric involvement or nodules situated beyond the boundary of the main mass is well known to both neuropathologist and neurosurgeon. Bi-hemispheric involvement and satellite tumor foci suggest a highly malignant glioma, especially anaplastic astrocytoma or glioblastoma.<sup>1,3,4</sup> Further, the removal of one lesion may only result in unfavorable shifts in intracranial pressure dynamics.<sup>1</sup> The following case report illustrates the ability of CECT to image bihemispheric tumor as well as satellite nodules situated beyond the main tumor mass. This CECT pattern is characteristic of highly malignant gliomas.

### CASE REPORT

A 67-year-old male realtor was in good health until 3 months before admission when he became tired, less concerned about personal hygiene, lost weight, and experienced a recent generalized convulsion. A radionuclide brain scan obtained three months before admission was interpreted as normal (Fig. 1). On admission he was described as confused, lethargic, but without localizing neurological signs. His confusion improved during the following 3 weeks, but his behavior continued to be inappropriate. After 3 weeks of hospitalization he left against medical advice, but was persuaded to have a computerized tomographic brain scan prior to returning home.

The positive CECT scan results led to immediate re-admission (Figs. 2 and 3). His general examination was again unremarkable, except for guaiac positive stools. For the first time, however, the neurologic examination disclosed mild right hemiparesis, nonfluent aphasia and a prominent snout and suck reflex. He continued to appear lethargic. There was no evidence of papilledema. The following day a bilateral carotid cerebral angiogram demonstrated avascular masses involving both frontal lobes without midline displacement (Fig. 5). Within the next 48 hours he became comatose, developed signs of transtentorial herniation and died shortly thereafter.

### CECT SCAN AND AUTOPSY CORRELATION

The brain was fixed in 10 percent formalin solution and cut in 13 mm. sections, approximately as

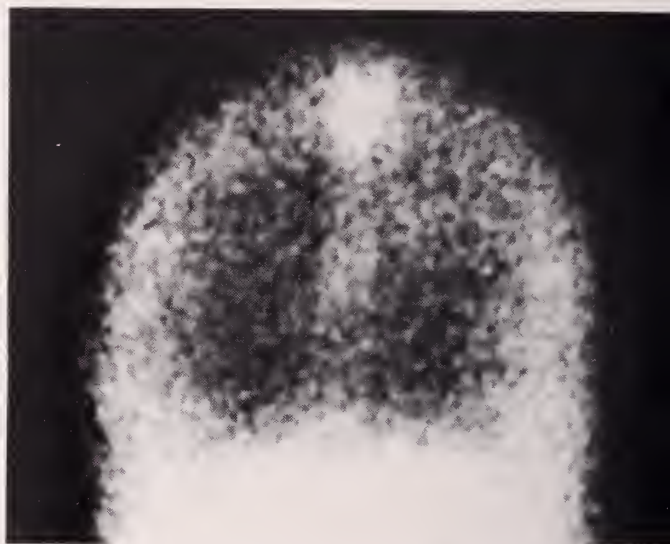


Fig. 1. "Normal" radionuclide brain scan obtained three months before admission.

closely as possible the planes of inclination of the CECT slices. Macroscopically, necrotic, hemorrhagic tumor was found in both frontal lobes with greater involvement on the left. The genu of the corpus callosum, anterior commissure, fornix and septum pellucidum were completely destroyed. The masses within both frontal lobes were poorly defined with conspicuous finger-like growths projecting from their margins. When sliced in cross-section these digitiform projections appeared as distinct nodules. An apparently independent very vascular tumor nodule was found within the white matter above the body of the left lateral ventricle (Fig. 4). This nodule was sharply delineated and only microscopic sections established histologic continuity with the main tumor mass beneath it. The contrast enhancement of this satellite nodule most likely resulted both from iodine within the vascular compartment as well as extravasation from a disrupted blood-brain barrier. This presumption was based both on the extensive vascular proliferation (vascular density 20 per mm<sup>2</sup>) and endothelial hypertrophy with perivascular hemorrhage found histologically.

### DISCUSSION

Early experience with non-contrast enhanced

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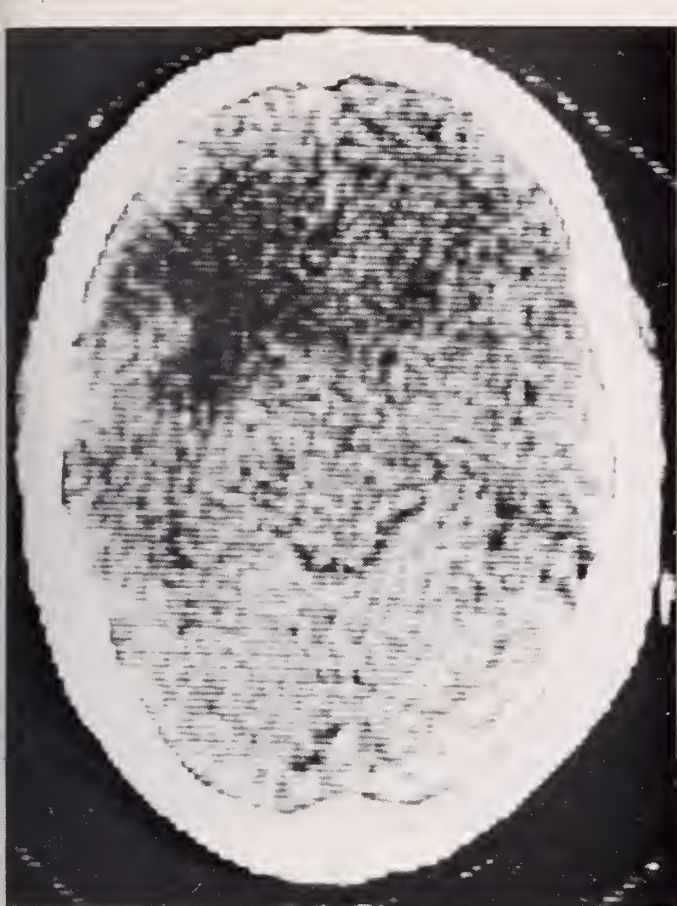


Fig. 2a

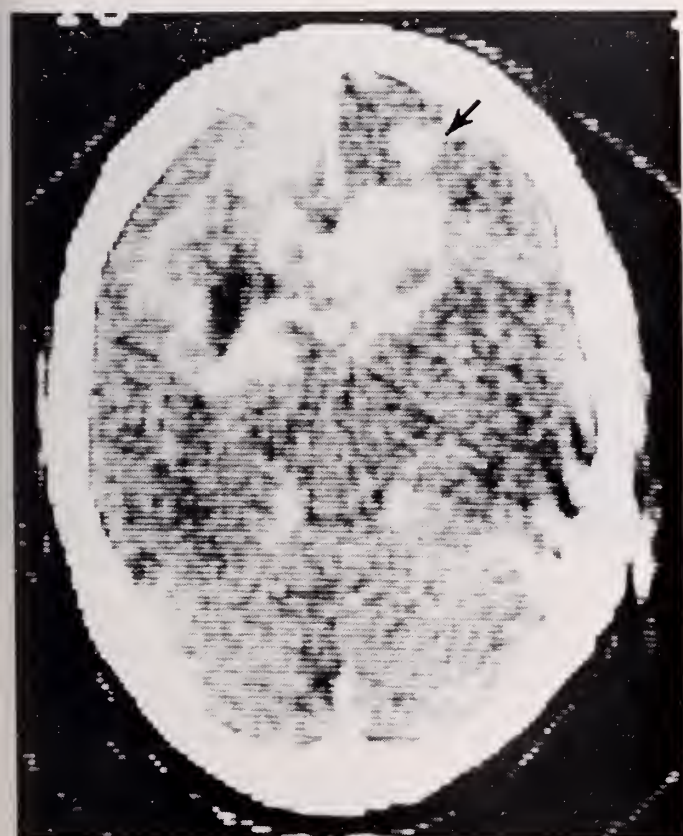


Fig. 2b

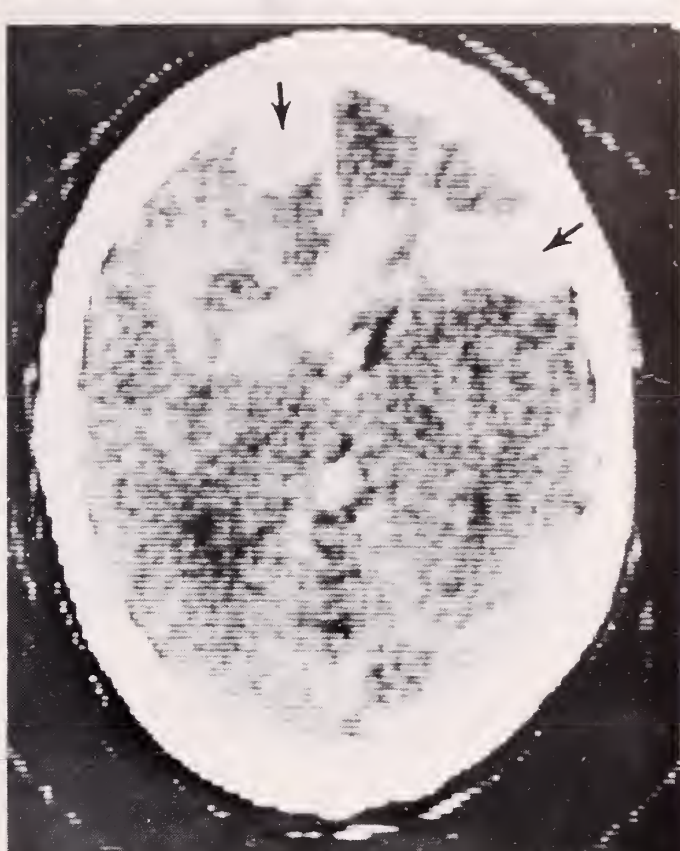


Fig. 2c

Fig. 2. C.T. scan demonstrating bifrontal glioma. A. Before contrast medium. B. and C. after contrast injection. Note enhancement of marginal satellite nodules (arrows).

computed tomography demonstrated its ability to suggest cystic, hemorrhagic and necrotic degeneration within mass lesions of the brain. CECT has added greatly to our *in vivo* visualization of tumor morphology, but to date careful studies comparing CECT images with pathologic growth patterns has not been published. As a preliminary to this important correlation, this report illustrates the capability of CECT to define highly malignant growth characteristics. Bi-hemispheric and marginal tumor foci were imaged by the use of intravenous iodinated contrast medium. In the past, neuropathologists have stressed the importance of growth patterns found at the margin of gliomas.<sup>5,6</sup> Many terms have been applied to multifocal patterns such as multicentric, multiple and satellite foci. Two or more foci may be found in different lobes of the same hemisphere or opposite hemispheres. Usually the mode of spread is macroscopically definable occurring by way of established pathways such as commissures, corpus callosum, fornix, internal capsule, massa intermedia, or cerebral spinal fluid spaces.<sup>1,3,7</sup> Bi-frontal glioma serves as the classic example. Occasionally, widely separated foci or satellite nodules are encountered where continuity with the main mass is only microscopically established. Completely independent foci with normal intervening tissue is quite rare.<sup>2</sup> Since these modes

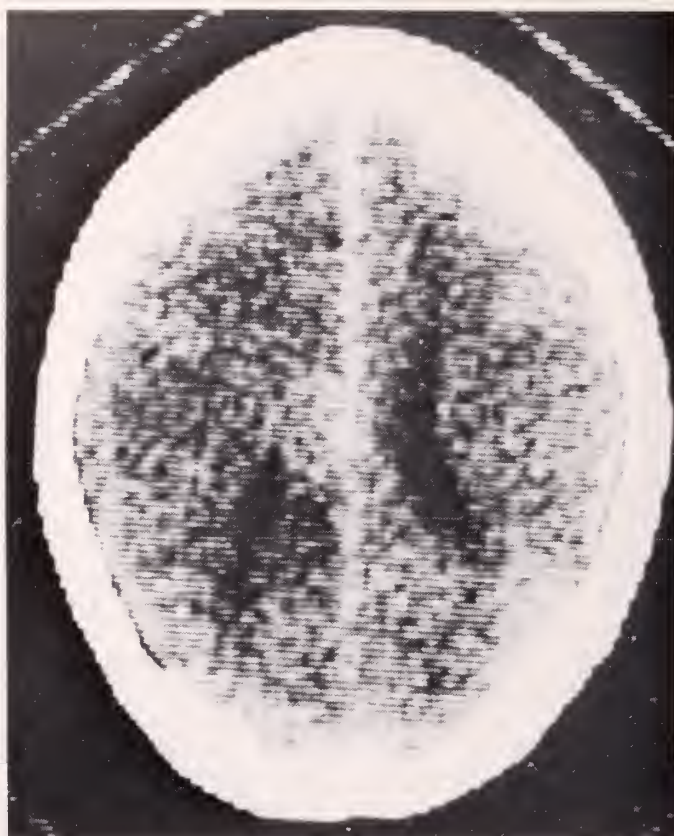


Fig. 3a

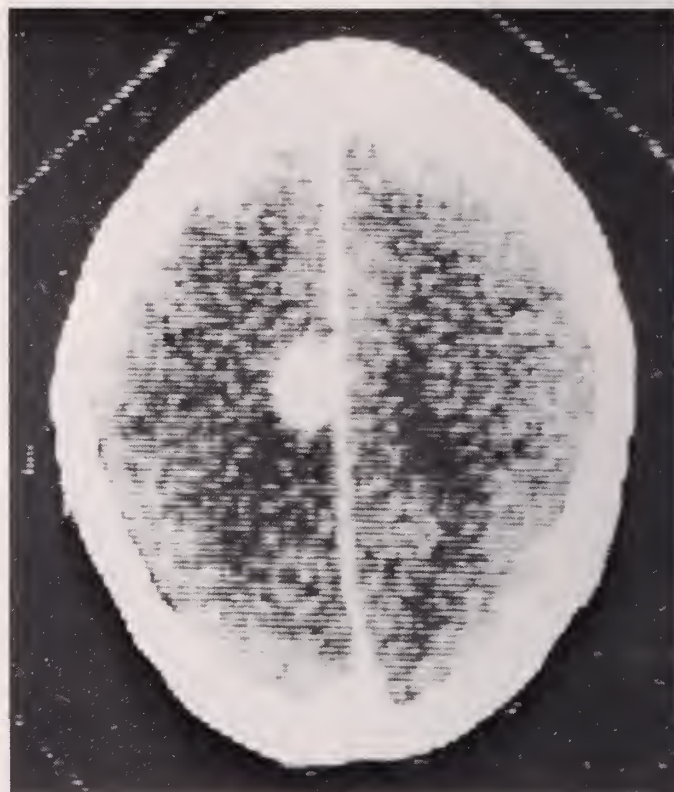


Fig. 3b

Fig. 3. Apparently independent nodule within white matter above the left lateral ventricle. A. Unenhanced scan. B. Contrast enhancement of A. Contrast medium given intravenously visualizes separate tumor nodule.



Fig. 4. Pathologic brain sections corresponding to CT slices of Fig. 3. Focal nodule (arrow) showed only histologic evidence of continuity with the main mass beneath it.

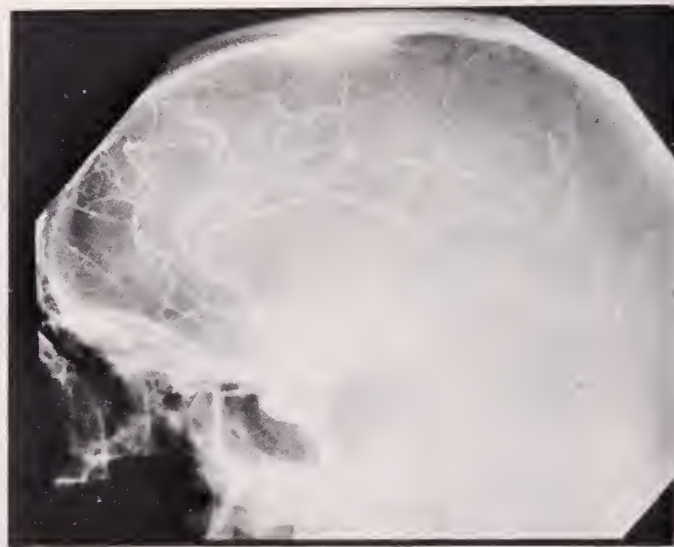


Fig. 5a

of growth are specific for highly malignant gliomas, especially anaplastic astrocytomas and glioblastoma multiforme, their *in vivo* recognition adds significantly to the management of primary brain tumors.

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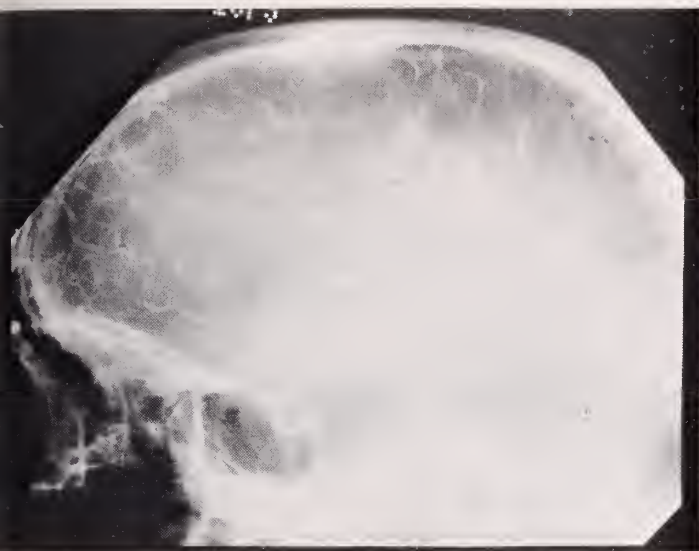


Fig. 5b



Fig. 5c

g. 5. Selective left carotid angiogram demonstrating the avascular nature of this highly malignant glioma. A. Early arterial phase showing only inferior displacement of middle cerebral arteries. B. Late capillary phase of arteriogram. No early veins demonstrated which are characteristic of high grade gliomas. Venous phase of angiogram illustrating the lack of tumor stain or prominent venous channels.

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## Workshop on Preceptorship Development

A Workshop for Physicians, Students, Medical School Faculty, and Program Directors

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### OBJECTIVES:

1. To share common preceptorship issues.
2. To pool ideas and knowledge for the development of an ideal preceptorship model.
3. To develop strategies to deal with key issues.

Approval expected for Category 1 AMA-CME Credits

# Clinical Staging of Chronic Lymphocytic Leukemia

DELVYN C. CASE, JR., M.D.\*

Chronic lymphocytic leukemia (C.L.L.) is malignant proliferation of normal appearing B-lymphocytes (bone marrow derived or Bursa-equivalent cells).<sup>1</sup> It is the most common leukemia in Western countries, occurring in an older population with particular clinical characteristics (Table 1).

C.L.L. is a disease known to have a variable course. It is not uncommon for patients to survive 10-25 years with often little therapy. Contrariwise, a proportion of patients succumb to infection, bleeding, or tissue infiltration within 1-2 years. The spectrum of disease is heterogeneous. Patients may present with only lymphocytosis or lymphocytosis associated lymphadenopathy, or hepatosplenomegaly, or anemia with/without thrombocytopenia. The anemia and thrombocytopenia may develop from peripheral destruction by a related autoimmune dyscrasia or from inhibition of normal development of hematopoietic elements by massive infiltration of the marrow with leukemic cells.

Response to treatment is variable. Therapy with alkylating agents usually chlorambucil can often lower the peripheral lymphocyte count in the majority of patients; but the response to treatment and the duration of response may be shortlived in the patients with advanced disease.

The staging of malignant disorders have allowed for the rational development of treatment programs. A notable development in the study of C.L.L. has been the formulation of a clinical staging system by Rai, et al<sup>2</sup> (Table 2). In addition to pathological lymphocytosis, patients are staged based upon the presence of lymphadenopathy, organomegaly, anemia, and thrombocytopenia. This staging system has been found to be directly related to prognosis by Rai, et al<sup>2</sup> and confirmed by the Memorial Sloan-Kettering group<sup>3</sup> (Table 3). Patients with stages O-II have the longest survival. Tissue infiltration in lymph nodes or liver and/or spleen (median survival 101 months and 71 months, respectively) lowers the median survival from that seen with only bone marrow and peripheral blood involvement (median survival > 150 months). For the patients presenting with anemia and/or thrombocytopenia, the median survival is only 19 months. The anemia and thrombocytopenia may be secondary to peripheral destruction from an autoimmune basis or to inhibition of red blood or megakaryocyte production by leukemic infiltration in the bone marrow. In this series hemolytic disease was not a better prognostic

TABLE 1

## CLINICAL CHARACTERISTICS OF CHRONIC LYMPHOCYTIC LEUKEMIA

Commonest leukemia
Incidence rises with age
Familial clustering
Fewest symptoms of the leukemias
Associated with hypogammaglobulinemia
Recurrent pyogenic infections common
Associated with autoimmune dyscrasias and diseases
Easiest leukemia to treat
Least likely of the leukemias to "blast off"
Longest survival of the leukemias

TABLE 2

## STAGING OF CHRONIC LYMPHOCYTIC LEUKEMIA<sup>2</sup>

Stage O	Lymphocytosis in peripheral blood (absolute count, $\geq 15,000/\text{mm}^3$ ) and bone marrow ( $\geq 40\%$ of nucleated cells)
Stage I	Lymphocytosis and lymphadenopathy
Stage II	Lymphocytosis and hepatomegaly and/or splenomegaly
Stage III	Lymphocytosis and anemia (Hemoglobin < 11 gm%)
Stage IV	Lymphocytosis and thrombocytopenia (< 100,000/ $\text{mm}^3$ )

TABLE 3

## MEDIAN DURATION OF SURVIVAL ACCORDING TO STAGE AT DIAGNOSIS<sup>2,3</sup>

Stage at Diagnosis	Median Survival (Mo.)
O	>150
I	101
II	71
III	19
IV	19
Overall	71

sign than bone marrow suppression of red cells or megakaryocyte production.

This staging system has implications for the choice of treatment of patients with C.L.L. In patients with predictable long survival, simple single drug therapy with an alkylating agent such as chlorambucil appears reasonable. Treatment of patients with Stages O-II with aggressive programs might produce excessive toxicity especially in this group of older patients where the outlook is already favorable.

The prognosis of patients in Stages III and IV is less encouraging. Single alkylating agents have had less lasting benefit in this group of patients. However, the experience with multiple drug regimens in this malignant disorder is limited. The few multi-

*Continued on Page 330*

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# Facial Ice Water Immersion

## A Noninvasive Treatment for Paroxysmal Atrial Tachycardia

W. PHELPS CARTER, JR., M.D.\*

The treatment of symptomatic paroxysmal atrial tachycardia (PAT) has historically involved initial noninvasive techniques as carotid massage and Valsalva's maneuver which have minimal side effects compared to pharmacologic agents like Edrophonium sulfate (Tensilon®), Propranolol (Inderal®), Methoxamine (Vasoxyl®). These drugs not only produce undesirable side effects but also require intravenous administration. The Diving Reflex method of PAT treatment by Wildenthal, et al<sup>1</sup> represents another therapeutic modality for the patient with PAT. Several cases have been treated successfully in the Department of Emergency Medicine. The technique is applicable for use in the private practitioner's office.

### CASE REPORT

L.W., a 54-year-old white male with a history of recurrent attacks of supraventricular tachycardia requiring vasopressor intravenous medications and quinidine prophylaxis in the past to maintain sinus rhythm, presented to the Department of Emergency Medicine with a history of "rapid heart beat" for approximately one hour. He had been on no medications for a month and denied excessive alcohol, tobacco or caffeine ingestion. In the past, the episodes of "rapid heart beat" had been associated with an occasional tight feeling in his chest. There was no chest pain, shortness of breath, or diaphoresis with this episode. His pulse was 160 and regular blood pressure 112/80 — EKG revealed supraventricular tachycardia with a rate of 160. P waves were noted prior to each QRS.

Carotid and Valsalva's maneuver failed to convert the rhythm. A pan of ice water was prepared and the patient was instructed to hold his breath without force and immerse his face in the ice water for as long as he could tolerate. His rhythm in twenty seconds of facial immersion converted spontaneously to sinus rhythm.

### TECHNIQUE

1. EKG determination of paroxysmal atrial tachycardia and monitor.
2. Historical contraindications: Angina Pectoris, recent myocardial infarction, multifocal PVCs, or history of ventricular fibrillation.
3. Attempt carotid massage and Valsalva maneuver.
4. Relax patient in upright position for several minutes.
5. Prepare large pan of ice water.
6. Have patient breathe deeply, lean forward while holding breath in inspiration, and immerse his face to the preauricular level in the pan for as long as he can tolerate the procedure.
7. Reassure patient that the procedure can be terminated at will but success depends on a minimum of 15 seconds.

### DISCUSSION

The diving reflex is a reflex mechanism which allows aquatic animals to stay submerged for long periods of time. Initially described by Irving, et al<sup>2</sup> in

seals, the reflex slows the heart rate, maintains arterial pressure and redistributes blood flow.<sup>3</sup> Wildenthal was the first to describe the applicability of this reflex to the treatment of PAT.

Two other noninvasive modes of therapy are carotid massage and Valsalva's maneuver.<sup>4</sup> Both rely on vagal stimulation to the heart slowing cardiac conduction. The response is decreased heart rate, hypotension, and reduction in cerebral blood flow. In the case of carotid massage, the decrease in cerebral blood flow not only from mechanical occlusion but also from vagal stimulation is hazardous in the elderly arteriosclerotic patient. Ventricular fibrillation has also been reported as a complication.<sup>5</sup>

Pharmacologic treatment involves vagal stimulation either by vasopressor agents raising the blood pressure with a reflex cardiac slowing or by directly increasing vagal tone by anticholinesterases (e.g., Tensilon®). Other intravenous medications are available and often produce pharmacologic side effects.

A common arrhythmia, PAT occurs in healthy young individuals with no demonstrable heart disease. Electrical impulses originating in an atrial foci override the SA node producing the rapid heart rate. Symptoms vary from complaints of palpitations, light-headedness, nausea, chest pain to the asymptomatic patient. As an arrhythmia in the healthy patient, it is rarely life threatening but can be refractory to treatment.

The diving reflex as proposed by Wildenthal<sup>1</sup> not only vagally stimulates cardiac depressor responses but also maintains blood pressure, contrary to other modes of therapy. The response appears to be mediated by thermoreceptors in the skin and baroreceptors in the chest. The result is vagal stimulation with a decrease in cardiac rate.

This physiological mechanism can be life-saving in the drowning victim by conserving oxygen demands. Hunt<sup>6</sup> relates the case of the successful resuscitation of a five-year-old child immersed in water 32°F (0°C) for half an hour. The child's hypothermia and diving reflex response were felt to be responsible for survival. Bradycardia during human diving has been extensively studied and is felt to represent a physiological protective oxygen conserving mechanism that allows humans to remain submerged for long periods of time.<sup>7</sup>

The preliminary reports by Wildenthal, et al relate seven cases (ages 22-66) who converted paroxysmal atrial tachycardia to sinus rhythm within 15-35 seconds after facial immersion in 2°C water while

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breath holding. The technique was employed on healthy subjects with no evidence of angina, myocardial infarction or ventricular irritability. The patients were monitored and sinus arrest was seen in one patient lasting 4-5 seconds. Other investigators have reported nodal and ventricular escape beats during conversion. Wayne<sup>8</sup> reports no arrhythmias during or after the procedure in ten patients. He reports a 90% success rate in nine out of ten patients with rapid conversion of PAT. The average conversion time was twenty-three seconds. Wayne used ice water at a temperature of 10°C. Investigations have found variability of response with water temperature.<sup>9</sup>

### CONCLUSION

Facial ice water immersion employing the diving reflex is a reliable noninvasive procedure for treatment of PAT. In the patient without contraindications, the technique results in rapid conversion of PAT to sinus rhythm. Self-administration of the technique in patients who have had a prior benign response under physician observation may have therapeutic implications. One patient has reported to me that he has employed the technique success-

fully at home. "Go soak your head"<sup>10</sup> despite its hostile connotation represents a reliable therapeutic modality for treating PAT.

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### CLINICAL STAGING OF CHRONIC LYMPHOCYTIC LEUKEMIA — Continued from Page 328

drug regimens reported have added little to survival. Recently, a program from the Memorial Sloan-Kettering Cancer Center using a five-drug regimen consisting of B.C.N.U., cyclophosphamide, vincristine, melphanlan, and prednisone has produced only a modest number of complete remissions;<sup>4</sup> but in the most recent analysis the median survival for the patients in Stages III and IV achieving complete (8%) and partial (54%) remissions might be prolonged compared with the results obtained with chlorambucil alone. Radiation therapy to the thymus has been shown in one paper to produce a high rate of excellent responses;<sup>5</sup> but these results could not be repeated in another series.<sup>6</sup> The therapeutic options in these patients are still less than satisfactory.

Further developments in therapy should be forth-

coming. The systematic staging of patients with C.L.L. will allow clinicians and investigators to approach the different groups of patients with logical treatment programs based upon the expected clinical pattern and survival.

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# Iatrogenic Ulnar Nerve Entrapment at the Elbow

JOHN J. ROACH, M.D., FACS\*

Learmonth pioneered the treatment of ulnar nerve entrapment at the elbow in 1942 with his technique of transplantation anterior to the medial epicondyle.<sup>1</sup> Over the years alternative techniques have developed for variations of olecranon ulnar palsy, such as medial epicondylectomy and/or decompression of the cubital tunnel.<sup>2,3</sup> These procedures have been effective in the hands of those surgeons able to identify the various constricting defects amenable to these alternatives. Only recently startling reports have been published as to the dangers of tardy ulnar neuropathy occurring after primary procedures where the nerve is left "in-situ." The hazardous points in secondary entrapment have been variously reported to be at the medial humeral intermuscular septum, at the entrance of the mass of the flexor carpi ulnaris, or at the position of a holding "sling suture."<sup>4</sup> Steroid injections seem to have no place in the treatment of the condition.<sup>5</sup>

## ANATOMY AND PATHOGENESIS OF ULNAR NERVE NEUROPATHY

On arising from the medial cord of the brachial plexus (C7, C8, T1), the ulnar nerve traverses the upper arm, medial to the brachial artery. Distally it

passes subfascially on the medial head of the triceps, traverses the elbow and enters the cubital tunnel. It then innervates the flexor carpi ulnaris and the ulnar portion of the flexor digitorum profundus. The palmar and dorsal cutaneous sensory branches exit next. In the hand, the intrinsic muscles, including the hypothenar and interossei, (the 4th and 5th lumbrical) and adductor pollicis, are innervated. Nerve impairment at the olecranon causes weakness of the flexor carpi ulnaris (wrist flexion), loss of lumbrical extension of the terminal phalanges of the 4th and 5th digits and impaired abduction-adduction of the fingers (interossei) (Fig. 1).<sup>6,7</sup> The familiar dorsal and palmar sensory loss of the ulnar innervation of the hand is also noted.

## CASE REPORT

On 5/5/75 S.H., a 37-year-old white rural home-health nurse underwent a transposition of the right ulnar nerve over the epicondyle and superficial to the flexor carpi ulnaris. Ulnar paresthesias for several months had existed and conduction studies were indicative of an olecranon ulnar neuropathy. The nerve was found to be "out of the groove and sitting on the medial epicondyle" — subluxation. Her symptoms subsided until December of 1976 when she rolled her automobile over on an icy Maine rural road. The same elbow was contused. Paresthesias with distal ulnar sensory loss developed. Abduction and adduction of the fingers and adduction of the thumb were lost with Froment's sign being present (Photograph 1). Six weeks were allowed to pass while the literature was reviewed with increasing alarm by the author.<sup>1,8</sup> Using a pneumatic tourniquet, reexploration on 1/31/77 found the nerve to be encased in a constricting fibrotic sheath in

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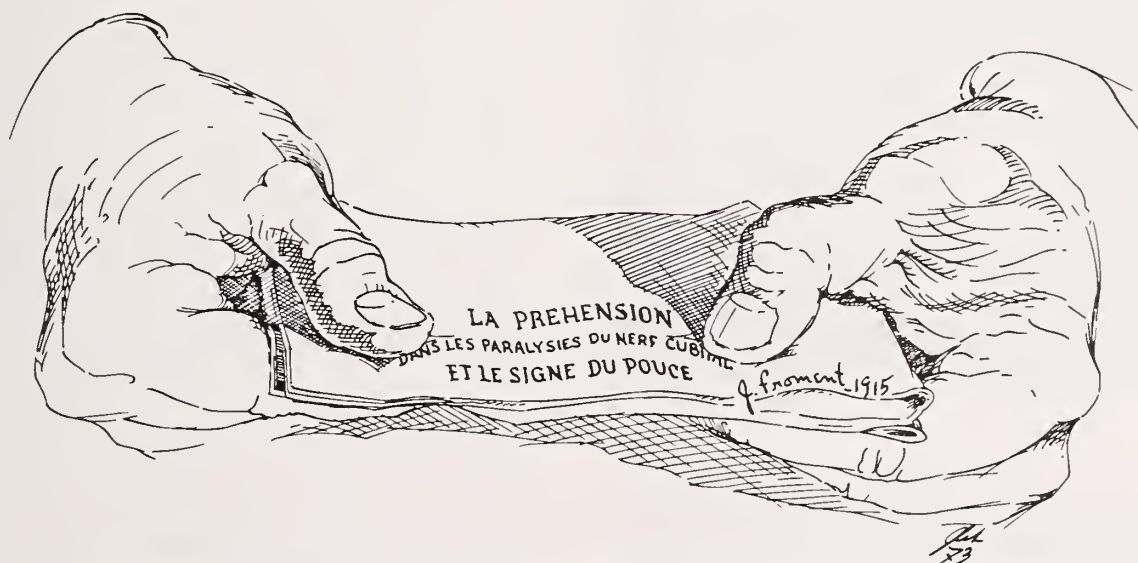
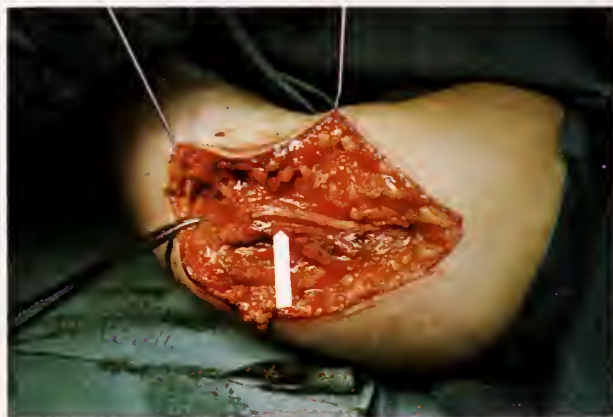


Fig. 1. Attitude of thumb with pinch prehension effort involving left ulnar nerve injury. Pinch power loss can be reduced from a normal of 25 to 5 pounds or less in some cases of flexor-adductor intrinsic muscle paralysis. The attending thumb weakness and attitude is known as Froment's sign.



(Photograph 1) Right intrinsic paralysis.



(Photograph 2) The arrow points to the opened fibrotic sheath. The clamp tip is at the cubital tunnel entrance. Note that the nerve is double its normal thickness in much of the proximal encasement. (The visual prospective is somewhat distorted by the camera lens.)



(Photograph 3) Anterior transposition of the ulnar nerve at the elbow.

the olecranon tunnel with no evidence that it ever had left this position. The fibrotic sheath was carefully excised taking great care of the microvascular system (Photograph 2). The medial epicondyle was transected with the common flexor origin and the nerve moved anterior to the epicondyle. The epicondyle was sutured back in place with fine wire sutures (Photograph 3) (Fig.

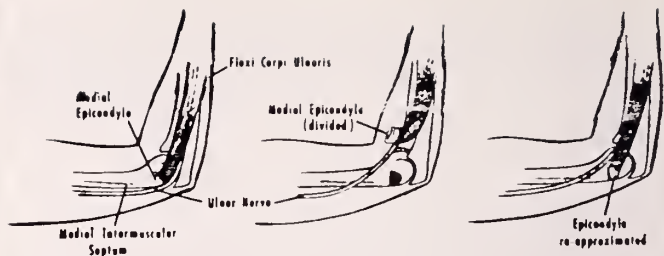


Fig. 2. The epicondyle and the origin of the flexor carpi ulnaris are retracted forward after division of the bone. The ulnar nerve is transposed laterally anterior to the epicondyle. The epicondyle is then reapproximated with several wire sutures. The result transposes the ulnar nerve anteriorly to the epicondyle and deep to the muscle group.

2).<sup>8</sup> Finally, the medial intermuscular septum was divided to prevent angulation in the upper arm. With flexion and extension of the elbow, the protection of the nerve and the gained length (5mm) could easily be visualized. The arm was casted in flexion for three weeks. No change in symptoms occurred until three days post-operatively when motor function returned rapidly followed by complete sensory return. Normal function was present on discharge from the hospital.

### COMMENT

It would seem that results from surgical procedures, in which the ulnar nerve is not transplanted deep to the origin of the flexor carpi ulnaris, must be carefully evaluated over a period of years. The scarring secondary to surgery and the danger of aggravating the scar with further trauma must be considered. Those people whose occupations result in unusual stresses to the elbow may not be candidates for the more conservative procedures (typists, truck drivers, draftsmen, baseball pitchers<sup>5</sup>). If a tardy ulnar neuropathy does develop, a good functional return can be expected with early exploration (within 12 weeks), but procrastination greater than six months may be detrimental.<sup>8,9</sup> The operation of choice would seem to be some form of transmuscular transplantation out of the olecranon groove and anterior to the epicondyle. Transplantation then allows the nerve to follow a more direct anterior course, surrounded by muscle, and protected by bone from further direct trauma.<sup>10</sup>

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*Continued on Page 344*

## Vasodilating Drugs and Their Use in Cerebral Symptomatology

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Drugs which increase blood flow by direct or indirect action on blood vessels are collectively called vasodilators. These drugs are used extensively to treat symptoms of peripheral vascular disease and symptoms believed secondary to insufficiency of cerebral vascular circulation. Coffman, in his recent review,<sup>1</sup> found little evidence of vasodilator drug effectiveness in obstructive arterial disease, but noted that certain agents which produce vasodilation by their effect on the sympathetic nervous system (reserpine and guanethidine) may, in some patients with peripheral vasospasm, increase cutaneous capillary flow. Vasodilator drugs are used for disorders known to be caused by cerebral vascular disease, such as transient ischemic attack and stroke. In addition, these drugs are now being used for what are frequently referred to as "grey area symptoms of the elderly," including confusion, lack of self care, dizziness, mood depression, and unsociability. These symptoms are erroneously attributed to cerebral vascular disease, but in reality they are related to a wide range of organic and psychological causes of cerebral dysfunction. This paper will review vasodilator drugs and their effectiveness in treating patients with cerebral vascular disease and "grey area" symptoms.

### VASODILATING AGENTS

The agents generally used for cerebral symptoms are:

1. Cycloandelate (Cyclospasmol®) — a mandelic acid ester of 3,5,5 trimethyl cyclohexanol. It acts on smooth muscle walls. The usual dosage is 400 to 800 mg daily.<sup>2,3</sup>
2. Isoxsuprine hydrochloride (Vasodilan®) — a synthetic agent with pharmacological action primarily on vascular smooth muscle.<sup>4</sup> It may increase cardiac contractility, heart rate, and cardiac output. Palpitations and postural hypotension are side effects.<sup>5</sup> The usual dosage is 30 to 60 mg daily.
3. Hydergine — obtained from the dehydrogenation of three alkaloids; it contains dihydroergocristine, dihydroergocryptine, and dihydroergocornine

in equal proportions. The drug has adrenolytic, direct vasomotor, and antiserotonin effects, and, in addition, it has a metabolic effect on ganglion cell metabolism.<sup>6</sup> The usual dosage is 3 mg sublingually daily.

4. Papaverine (Cerespan®, Pavabid®, Vasospan®, Pavacap®, Pavacen®) — a member of the benzylisoquinoline group of alkaloids found in opium; it can be made synthetically. Papaverine produces vasodilation by a direct action on arterial smooth muscle, and it causes a decrease in cerebral vascular resistance and an increase in cerebral vascular flow.<sup>7</sup> It may be associated with arrhythmias after intravenous injection.<sup>8,9</sup> The usual dosage is 300 to 600 mg daily.

5. Nicotinic acid (Nicobid®, Roniacol®) — a pyridine-3-carboxylic acid acting on smooth muscle. The usual dosage for Nicobid is 250 to 2000 mg daily; Roniacol, 150 to 600 mg daily.

Drugs which primarily reduce sympathetic nervous system activity — tolazoline hydrochloride (Priscoline®), phenoxybenzamine hydrochloride (Dibenzyl®), and guanethidine sulfate (Ismelin®) — have had no place in the treatment of cerebral vascular disease except when used to treat coexisting hypertension. Vasospasm does not play a role in ischemic cerebrovascular disease; however, vasospasm is present in patients who have had subarachnoid hemorrhage and is produced by direct action of blood products on the cerebral vessels in the subarachnoid space.

### CEREBRAL BLOOD FLOW

A knowledge of cerebral blood flow, its measurement and abnormalities, is an important prerequisite before considering effects of treatment designed to alter cerebral hemodynamics.

In 1945, Kety and Schmidt described a method to measure cerebral blood flow in man.<sup>10,11</sup> Nitrous oxide was inhaled for 10 minutes with subsequent sampling of arterial and jugular venous blood each minute; total cerebral blood flow was calculated using the Fick principle previously applied for measurement of cardiac output. Since 1945, the methodology has greatly improved and now allows the estimation of blood flow to a particular region of the brain.

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Advanced methodology involves injecting radioisotopes (usually  $^{133}\text{Xe}$  or  $^{85}\text{Kr}$ ) into the internal carotid artery of a patient at the time of cerebral angiography; external scintillation counters placed on the scalp monitor local clearance of the isotope. A calculation of regional cerebral blood flow (rCBF) in both grey and white matter under the probe can then be made for each region monitored.<sup>12</sup> By comparing the abnormal region in a stroke patient with the same area in the normal hemisphere of the same patient, one can study the effects of the stroke.

Changes produced by alterations in blood pressure, inhalation of carbon dioxide, and injection of pharmacological agents such as vasodilator drugs can subsequently be monitored in the region of abnormal blood flow. In addition, laboratory experimentation using these cerebral blood flow and autoradiographic techniques can be applied to normal animals and animals in whom cerebral ischemia has been produced.<sup>13,14</sup> Thus, it is now possible to selectively measure blood flow parameters in the area of the brain deprived of blood.

Information on normal and ischemic blood flow can be summarized as follows:

1. Regional cerebral blood flow is abnormal in most individuals with stroke<sup>12,15</sup> and in some patients with transient ischemic attacks.<sup>16</sup> The abnormality may be either a reduced rCBF (averaging approximately 32%)<sup>15</sup> or an increased rCBF (reactive hyperemia).

2. Prognosis for recovery from stroke is generally not related to the degree or type of change in rCBF.<sup>15</sup>

3. Hyperemic change in patients with stroke is felt to be secondary to local metabolic changes, especially accumulation of lactic acid; hyperemia may occur within the ischemic region or in the region surrounding it.<sup>17,18</sup>

4. Normal cerebral circulation has the capacity for autoregulation. Johnson defined autoregulation as "the intrinsic tendency of an organ to maintain constant blood flow despite changes in arterial perfusion pressure."<sup>19</sup>

5. The stroke patient frequently loses autoregulation in the region of the stroke.<sup>15,20</sup>

6. In normal patients rCBF increases when carbon dioxide is inhaled; in stroke patients responsiveness of the local region to alterations in  $\text{pCO}_2$  is frequently lost.<sup>15,20,21</sup>

7. The loss of normal reactivity of blood vessels in the region of stroke (loss of autoregulation and carbon dioxide reactivity) may be secondary to ischemic damage to the local blood vessels. In addition, there are local metabolic changes which favor maximal vasodilation — the local vascular system may lose its capacity to further dilate.<sup>20</sup>

8. Some stroke patients exhibit a paradoxical response to carbon dioxide inhalation. In these patients carbon dioxide augments blood flow to normal regions where vessels retain their reactivity, but blood flow falls in regions that have lost their reac-

tivity. Thus, when carbon dioxide is inhaled,<sup>20</sup> blood travels away from the needed region toward normal areas. This phenomenon is more common in the acute phase of the stroke and is rare later.<sup>19,21</sup>

9. The abnormal response of the cerebral circulation in patients with stroke has led to the prediction that vasodilator therapy (either carbon dioxide or pharmacological agents) would be ineffective and possibly harmful in acute apoplexy. Because it is more effective in normal regions and less effective in the region of vasomotor paralysis, the vasodilator could shunt blood away from an ischemic focus.<sup>13</sup>

#### VASODILATOR AGENTS AND CEREBRAL BLOOD FLOW

Papaverine relaxes smooth muscle throughout the body and produces a decrease in cerebral vascular resistance and an increase in cerebral blood flow.<sup>22</sup> Thus, papaverine produces cerebral vasodilation by acting directly on arterial smooth muscle. This was demonstrated in a variety of animal experiments.<sup>23</sup> Jayne, Scheinberg, and Rich demonstrated that intravenous papaverine could augment total cerebral blood flow (as measured by the Kety-Schmidt technique) in patients without cerebrovascular disease by 13% after 20 minutes.<sup>24</sup> Aizawa, Tezaki, and Gotoh reported an increase in cerebral blood flow after intravenous papaverine was infused in seven patients.<sup>25</sup> However, Shenkin reported no change in blood after papaverine was infused in four patients using a smaller intravenous dose.<sup>26</sup> McHenry and coworkers demonstrated an 18% increase in mean cerebral blood flow after infusing papaverine in six patients and found a significant increase in regional cerebral blood flow in eight and a decrease in one of 20 ischemic regions.<sup>27</sup> However, papaverine failed to alter the clinical course of the stroke patients.

Papaverine, when given intravenously, may produce the unwanted effects of hypotension, drowsiness, apprehension, and thrombophlebitis at the site of injection. I was unable to find studies on the effect of orally-administered papaverine on regional cerebral blood flow in patients with stroke.

Papaverine has been used in an attempt to prevent cerebral vasoconstriction due to operative stimulation of cerebral blood vessels.<sup>28</sup> Some authors feel that postural hypotension would limit the use of papaverine in ambulant patients.<sup>29</sup>

Blood flow studies of other vasodilator agents are quite scanty. Hexobendine (an experimental drug) was shown by Meyer and colleagues to increase blood flow in the normal and ischemic cerebral hemisphere of stroke patients despite a fall in mean arterial blood pressure.<sup>30</sup> The agent was less effective orally than intravenously. McHenry, using rCBF techniques, found that parenterally administered Hydergine did not change cerebral blood flow in stroke patients.<sup>31</sup>

Experimental studies have shown that, occasionally, an agent expected to function as a cerebral vasodilator (eg, aminophylline) actually produces

fairly potent cerebral vasoconstriction in normal brain vessels.<sup>32</sup> This observation underlines the need for measuring cerebral blood flow when evaluating the effect of pharmacological agents on the cerebral circulation.

There is a paucity of data regarding the effect of vasodilator agents on cerebral blood flow. The available data suggests that intravenous papaverine and hexobendine augment regional cerebral blood flow in some patients, but whether or not the effect will be clinically useful is unclear.

#### **VASODILATING AGENTS IN STROKE OR TRANSIENT ISCHEMIC ATTACKS**

The value of vasodilator treatment in stroke patients is questionable for the following reasons:

1. The abnormal or paradoxical responsiveness of cerebral circulation in stroke patients renders vasodilator treatment ineffective, and in some cases harmful.

2. Cerebral vessels have a scarcity of elastic fibers in the media and may be less responsive than systemic vessels. Therefore, vasodilator agents may produce more systemic vasodilation than cerebral; this could lead to postural hypotension. Headache and faintness have been noted after inhalation of glyceryl trinitrate, a known vasodilator.<sup>33</sup>

3. Vasospasm has not been associated with occlusive cerebrovascular disease. The only known disorders related to cerebral vasospasm are migraine, disorders caused by intravenous drug usage, subarachnoid hemorrhage, disorders caused by manipulation of brain tissue and its vessels, and hypertensive encephalopathy.

Data concerning the use of various vasodilator agents on patients with well documented stroke or transient ischemic attacks (TIA) is scanty. Many studies utilize patients with vague symptomatology not clearly related to cerebrovascular disease, and fail to provide adequate controls.

Eichorn studied the use of cyclandelate in 20 patients, using a placebo in 20 other patients as a control.<sup>34</sup> Unfortunately, this was a heterogeneous group of patients, many with the diagnosis of "hypertensive encephalopathy," and the makeup of each study group was not detailed. Radiocirculography, which measures the rate of arrival in the cerebral vessels of an isotope injected into an arm vein, was the objective parameter Eichorn used to study cerebral circulation. Radiocirculography is a non-specific test which cannot measure regional flow. The reported benefit of cyclandelate was based on the improvement of subjective symptoms. According to Eichorn "Very severe cases of arterial insufficiency did not respond as well [as less severe cases] or not at all."

Van der Drift used cyclandelate in 200 patients, 175 with ischemic attacks and 25 with stroke.<sup>35</sup> Eighty of these patients received other treatment (reserpine, ephedrine, anticoagulants). There were no controls. Seventy-two of 120 cases taking cy-

clandelate alone in doses of 200 to 600 mg daily showed "good to marked" improvement. But this is an uncontrolled, poorly documented group of patients. It is impossible to differentiate the results from the natural history of the disease studied.

Gilroy and Meyer studied 70 patients who had suffered progressing strokes of less than 72 hours duration.<sup>36</sup> Thirty-four patients, chosen randomly, were given 500 mg of papaverine in saline over an eight hour period (alternating treatment periods of eight hours with eight hours of no therapy for 10 days). Five patients died (two treated, three control), seven deteriorated (two treated, five control), nine were unchanged (five treated, four control), and 49 improved (25 treated, 24 control). In an intricate point scoring system those with treatment had a higher number of points (124), meaning a greater degree of improvement, than the control patients (77) after 10 days. Patients treated with papaverine showed no serious side effects. The difference between the two groups was small, and Rheinmuth, in discussion of the paper, felt that the two groups might not have been identical prior to treatment.<sup>37</sup>

#### **VASODILATING AGENTS IN SENILE OR PSYCHIATRIC PATIENTS**

Most of the clinical studies of vasodilator treatment in senile or psychiatric patients involve a heterogeneous group of elderly patients frequently from psychiatric institutions, with senile dementia, confusional states, and, at times, depression. This group is often referred to as suffering from "cerebral arteriosclerosis." Senile dementia, the most common neurological disorder of the elderly, is an atrophic disorder pathologically characterized by selective grey matter atrophy and neuronal loss beginning in parietal, frontal, and hippocampal regions, accompanied by senile plaques and neurofibrillary degeneration. There is ample evidence that this common disease has nothing to do with "cerebral arteriosclerosis," though the terms "hardening of the arteries" and "senility" are considered synonymous in lay and some medical circles. Confusional states are seldom related to arteriosclerosis but generally result from a variety of toxic, psychological, and metabolic factors (drugs, cardiopulmonary, nutritional). There has been some documentation of diminished cerebral blood flow in patients with senile dementia, but this is secondary to the decreased metabolic demand of the reduced volume of grey matter; that is, the reduced flow is a result and not the cause of the condition.

Psychiatric institutionalized patients are notoriously difficult to evaluate. Subjective evaluation parameters such as "brightness," "restlessness," "suspiciousness," "mannerisms," and "cooperativeness" are vague. Objective parameters are few; even objective psychometric testing varies with mood and effort, and an electroencephalogram, a frequently chosen "objective test," has little to do

TABLE 1.

RESULTS OF A STUDY OF HYDERGINE IN SENILE PATIENTS<sup>39</sup>

	Percent of	
	Patients Improved	
	Hydergine	Placebo
Hostility	86	41
Dizziness	77	58
Bothersomeness	69	58
Irritability	67	48
Confusion	64	28
Uncooperativeness	64	40
Mood depression	61	32
Unsociability	60	30
Impaired recent memory	60	40
Impaired mental alertness	56	40
Indifference to surroundings	54	44
Anorexia	54	23
Anxiety	54	54
Impaired self-care	50	30
Impaired motivation and initiative	48	36
Emotional lability	44	34
Fatigue	40	25

with intellectual or functional performance.

Institutionalized patients and some other groups of elderly demented patients clearly suffer from lack of attention. In these groups support, interest, enthusiasm, testing, and any new treatment, generally has a profound influence on mental condition. Therefore, the placebo effect is great.

It would not be useful to describe each study of vasodilators in the treatment of grey area symptoms. Accordingly, a few examples will be cited in

order to describe the essential nature of these studies.

Dhrymiotis and Whittier studied the use of isoxsuprine hydrochloride on 32 state mental hospital patients suffering from "chronic brain syndrome with psychotic reaction."<sup>38</sup> Symptoms included visual or hearing abnormalities, dysarthria, dysphagia, weakness, paresthesias, convulsions, headache, dizziness, disorientation, and changes in levels of consciousness. A crossover technique was used in which placebo and isoxsuprine were used for six months. Ward personnel and a research nurse evaluated the drug's effect upon patients. Fewer "episodes" were noticed during the drug period (almost completely related to decreased complaints of headache and dizziness). The differences were "not significant when tested statistically." No changes were observed in mental state, behavior, or face-hand test in any of the patients, nor were there drug side effects. The stated conclusion of the study is "... that the human cerebral vascular system is capable of vasospasm with some symptomatic manifestations, and that this vasospasm is preventable by isoxsuprine medication."

Winslow treated 50 institutionalized patients (average age, 77 years), with moderately impaired behavioral and cognitive function, with either placebo or 3 mg of Hydergine.<sup>39</sup> The percentage of patients who improved on either treatment is shown in Table 1. The high placebo effect and subjectivity

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of symptoms is readily apparent.

Bazo studied 66 patients whose average age was 85 years and average stay in a nursing home was greater than four years.<sup>40</sup> Those on Hydergine<sup>®</sup> had a global therapeutic change of 0.44 as compared to 0.18 with papaverine, with greatest improvement in depression, alertness, confusion, and emotional lability.

Triboletti and Ferri,<sup>41</sup> Roubicek, Gerber, and Abt,<sup>42</sup> and Rao and Norris<sup>43</sup> all studied the effects of Hydergine on institutionalized aged patients and all found a significant improvement in general symptoms of behavior and sociability.

Nelson, studying both hospitalized and office patients, found 86% of the patients on Hydergine and 55% on papaverine improved.<sup>44</sup> Furthermore, Nelson reported that patients taking Hydergine "generally reported that they felt better and that they were more alert."

Shader and Goldsmith have reviewed recent studies utilizing papaverine and Hydergine in general psychological symptoms of the elderly.<sup>45</sup> They found that placebo, papaverine, and Hydergine all produced improvement over a seven week period, but after the seventh week the placebo group no longer improved.

I find it difficult to interpret the data concerning vasodilating agents and non-specific mental symp-

toms of the elderly. The beneficial effects are vague, difficult to quantitate, and of questionable functional significance. There is considerable variability in the percentage of Patients improved for a specific symptom by the same drug in different studies. Further, in some studies  $p < 0.1$  is considered significant.

## CONCLUSIONS

There is insufficient data concerning the effectiveness of vasodilator drugs in patients with stroke. Stroke is a general term which describes a variety of different types and severities of cerebral vascular disorders. It is unlikely that any one treatment will have a salutary effect on all forms of cerebral vascular occlusive disease. New technology now makes it possible to study cerebral circulation in a more complete way.\* Studies on the use of various agents (including vasodilator drugs) in subcategories of stroke are badly needed.

At present, there is little to recommend the use of vasodilator agents for nonspecific cerebral symp-

\*Computerized axial tomography can document the presence of infarction and exclude hemorrhage; magnification angiography can better elicit the locale, type, and severity of occlusive vascular disease, and better techniques of measuring and studying regional cerebral blood flow are available.

toms of the elderly. More studies are needed using vasodilator drugs in patients who have been placed in clear diagnostic categories, eg, senile dementia, depression, metabolic encephalopathy, multiple cerebral infarctions. Evaluation should include careful standard psychometric testing and neurological examinations before and after treatment. The effect of vasodilators should be compared to placebos, tranquilizers, and antidepressants in a group of patients within a single diagnostic category.

Clinical neurologists have defined some treatable causes of dementia and confusion in the elderly. Frequently these disorders require specific investigation and testing for their recognition. Examples of these conditions include: 1) metabolic disorders (pernicious anemia, hypothyroidism, hypercalcemia); 2) drug toxicity; 3) normal pressure hydrocephalus; 4) brain tumor, particularly meningioma; 5) unrecognized depression; and 6) infection of the nervous system. The use of a drug allegedly helpful in *all* cases of confusional states of the elderly, irrespective of etiology, may delay more definitive and more important evaluation with subsequent specific treatment. In principle, physicians and pharmacologists agree that rational use of an agent to treat a disease process or a known disordered pathophysiology is far preferred to treatment of a symptom.

Until it is clearly shown that vasodilating drugs change functional capacity, promote more effective social behavior and self-care at home, or allow a patient to leave a nursing home or hospital or to move within a care facility to a region requiring a greater degree of self-care, there is little to gain by their use.

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*Continued on Page 344*



## CARTER CAP DISCUSSED

At a recent public hearing in Bangor, Vice President of Research and Provider Affairs, Thomas W. Cathcart, testified before the Senate Finance Committee on S. 1391, the Carter Administration's proposal to cap hospital costs.

Cathcart's testimony read:

"Blue Cross and Blue Shield of Maine provides prepaid health care coverage for over 541,000 Maine people, or about 1 out of every 2 people in the State. We are also the fiscal intermediary for Part A of Medicare for most of the institutional providers in Maine.

"We at Blue Cross and Blue Shield of Maine have directly felt the impact of the rising cost of inpatient care. In the first quarter of 1977, per diem benefits were up 24.9% over the first quarter of 1976. Second quarter figures do not look any more promising. Increases of this magnitude are putting a severe strain on our subscribers' ability to pay. We have been accused recently of exorbitant rate increases for Blue Cross coverage — but, of course, these rate increases merely reflect the rising cost of hospitalization.

"The hospitals say that a day of hospitalization this year is a different product from a day of hospitalization last year, and that is unquestionably true. According to the American Hospital Association, the rise in the cost of a day in the hospital is nearly equally divided between: (1) a rise in the prices hospitals must pay for goods and services; and, (2) an increase in the *intensity* of care. In other words, nearly half of the rise in costs last year was because *more* care is given in a typical hospital day.

"But even if more intense care could be shown to necessarily be better care, the question would still remain as to how long we can continue to pay for hospital care at a rate rising well in excess of the rate of rise in the cost of living. Not too many years ago Americans paid about 5% of personal income for health care. Now we pay nearly 10%. Can we afford 15%? 20%? At what point do national expenditures for health care begin to drain resources from other national priorities — some of which have an impact on health — priorities such as housing, nutrition, education?

"It has been our hope that a proposed voluntary prospective reimbursement pilot program involving Blue Cross of Maine and a number of Maine hospitals will have a favorable impact on the cost spiral in Maine. We continue to have that hope. We have received a letter of commitment from a committee of the hospital association to work with us toward that end. We must admit, however, that a voluntary pilot program in Maine does not do much to solve a national problem. And we must further admit that it will be some years before our pilot program can be developed, implemented, and evaluated. Therefore, while we will continue to pursue the course of developing a voluntary prospective reimbursement pilot program in Maine, we reluctantly find ourselves in support of a transitional limit on the rate of increase in hospital inpatient revenues. We do not feel that such a limit is a sound long-term solution, but we can endorse it as an interim step until permanent reforms can be effected.

"Likewise, the provisions regarding capital expenditures in Title II of the bill seem to us worthy of endorsement as transitional measures. A long-term solution should include decertification of excess capacity with a provision to protect the creditors of the institution.

"The bed ceiling of 4 beds per 1,000 population is of interest in Maine where we have more than 4½ beds per 1,000 people. Recently the Health Systems Agency — justifiably and with Blue Cross' support — approved 20 additional beds in Rockland. This might have been problematic had S.1391 been in effect. There is an exception procedure to the 4 beds per 1,000 provision of the bill. We would hope that this exception procedure would not be too cumbersome.

"In summary, then, Blue Cross and Blue Shield of Maine feels forced to endorse S.1391 as a transitional cost containment measure for hospitals. We hope that Congress and the Administration will follow quickly with long-term reforms."

President  
Maine Medical Association  
1977-1978



DOUGLAS R. HILL, M.D.

Douglas R. Hill, M.D., of South Portland, Maine, became the 128th President of the Maine Medical Association at the 124th annual session banquet on June 13, 1977. He has represented the Second District on the Executive Committee of the Maine Medical Association since 1974, serving as Chairman for 1976-1977.

Dr. Hill was born in Portland on April 22, 1927, son of Carlos L. and Vivian L. Hill. He was graduated from South Portland High School in 1945, Bowdoin College in 1950, and received his medical degree from the University of Rochester School of Medicine in 1954. Following an internship and residency at the Rhode Island Hospital in Providence, Dr. Hill began practice in South Portland. He is certified by the American Board of Family Practice.

He is a member of the Cumberland County Medical Society (and former Secretary-Treasurer and President), the Maine Medical Association, the American Medical Association, the American Academy of Family Physicians, and is President of the Maine Chapter, American Academy of Family Physicians.

Dr. Hill, his wife and children reside in Cape Elizabeth.

Executive Committee Members Elected at the  
124th Annual Session of the Maine Medical Association  
Rockport, Maine

June 11-14, 1977

*President*  
DOUGLAS R. HILL, M.D.  
South Portland

*President-elect*  
FRANCIS I. KITTREDGE, M.D.  
Bangor

*Eighth District*  
CHARLES H. LIGHTBODY, M.D.  
Guilford

*Second District*  
WILLIAM H. MAXWELL, M.D.  
Portland

*Delegate to the AMA*  
ROBERT E. MCAFEE, M.D.  
Portland

*Third District*  
JOHN W. WICKENDEN, M.D.  
Rockland  
*Executive Committee Chairman*

*Alternate Delegate to the AMA*  
BRINTON T. DARLINGTON, M.D.  
Augusta

*Seventh District*  
ROSS W. GREEN, M.D.  
Lewiston

*Speaker of the House*  
GEORGE W. BOSTWICK, M.D.  
Newcastle

Dr. Francis I. Kittredge was elected President-elect; Dr. George W. Bostwick, Speaker of the House; Dr. Robert E. McAfee, Delegate to the AMA and Dr. Brinton T. Darlington, Alternate Delegate to the AMA. The following physicians were elected to the Executive Committee: Dr. William H. Maxwell, Second District (1977-1978), to complete Dr. Douglas R. Hill's unexpired term; Dr. John W. Wickenden, Third District (1977-1980), and *Chairman* (1977-1978); Dr. Ross W. Green, Seventh District (1977-1980); and Dr. Charles H. Lightbody, Eighth District (1977-1980).

DR. KITTREDGE, of Bangor, was born in Philadelphia, Pennsylvania on November 8, 1934, son of Francis I. and Mary M. Kittredge. He was graduated from the University of Notre Dame in 1956 and received his medical degree from Temple University School of Medicine in 1959. He served in the U.S. Army as a Captain from 1959 to 1962, interned at the Martin Army Hospital in Georgia, served a residency in Neurology at the Pennsylvania Hospital and took a postgraduate course at Temple University School of Law. Dr. Kittredge located in Bangor in 1972 where he is affiliated at the Eastern Maine Medical Center (Chief of Neurology), St. Joseph Hospital and J. A. Taylor Osteopathic Hospital (consulting).

He is a member of the Penobscot County Medical Association, the Maine Medical Association, the American Medical Association and the M.M.A. Committee on Legislation.

Dr. Kittredge is a member of the Commission to Revise the Laws Relating to Medical and Hospital Malpractice Insurance, Vice Chairman of the Joint Underwriting Association, Associate Editor of the Journal of Legal Medicine, member of the Maine State Bar, Federal Bar, American and Maine Bar Associations, American Trial Lawyers Association and Maine State Trial Lawyers Association.

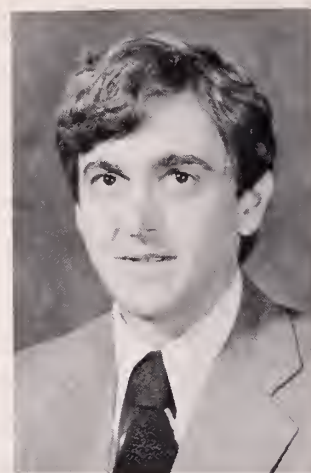
DR. MAXWELL, of South Portland, was born in Portland on February 16, 1939, son of Irving W. and Florence D. Maxwell. He was graduated from Middlebury College and received his medical degree from Boston University School of Medicine in 1966. He interned in Surgery at Boston University Medical Center from 1966 to 1967, served in the U.S. Army as a Captain from 1967 to 1969 and served a residency in Surgery



DR. KITTREDGE



DR. MAXWELL



DR. WICKENDEN

and ENT from 1970 to 1973. He located in South Portland in 1973 and is on the active staff at the Maine Medical Center and Mercy Hospital and on the consulting staff at the Bridgton Hospital.

He is a member of the Cumberland County Medical Association, the Maine Medical Association and the American Medical Association.

DR. WICKENDEN, of Rockport, was born in New Haven, Connecticut on August 16, 1940, son of Grover B. and Olwen W. Wickenden. He was graduated from Yale University in 1962 and received his medical degree from Yale University School of Medicine in 1966. He served a rotating internship at San Francisco General Hospital from 1966 to 1967 and served the first year of his residency in Orthopedic Surgery at the Long Beach (California) Veteran's Hospital from 1967 to 1968. He was in the U.S. Army Medical Corp at Fort Hood Army Hospital (Texas) for two years, retiring as a Major, and receiving the Army Commendation Medal, in 1970. He completed his orthopedic surgery residency at Yale University in 1972. He has practiced in Rockland since that time.

He is a member of the Knox County Medical Society, the Maine Medical Association, the American Medical Association, and the Maine Academy of Orthopedic Surgeons. He is certified in orthopedic surgery by the American Board of Orthopaedic Surgery and is a Fellow of both the American Academy of Orthopaedic Surgeons and the American College of Surgeons.

Dr. Wickenden is affiliated with the Penobscot Bay Medical Center where he is also the Medical Director of its Skilled Nursing Facility. He is on the consulting staff (Orthopedic Surgery) at the Waldo County General and Miles Memorial Hospitals.

His major interest outside of Orthopedic Surgery is politics, both medical and the Republican party. He has been a director of several Knox County community service organizations including the Y.M.C.A. and Project Grow. He is married and has two sons.

Dr. Wickenden has been a member of the Executive Committee of the M.M.A. for the Third District since 1975 and was elected chairman of that committee in June 1977.

DR. GREEN, of Lewiston, was born in Summerside, P.E.I., Canada on October 8, 1916. He attended the University of Virginia, graduated from Boston University, and received his medical degree from Tufts University School of Medicine in 1944. He interned at the Boston City Hospital and his postgraduate courses include: Surgical Resident at the Boston City Hospital, the Memorial Hospital in Worcester, the Pondville Cancer Hospital in Walpole and Surgical Assistantship to Dr. William V. Cox at the Central Maine General Hospital in Lewiston. In 1950, he located in Auburn and practiced there until 1973 when he moved his office to Lewiston. He has been certified by the American Board of Surgery.

He is a member of the Androscoggin County Medical Society and the Maine Medical Association, and serves on the Ad Hoc Burn Advisory Committee of the M.M.A.

DR. LIGHTBODY, of Guilford, was born in Waterville, Maine on April 15, 1925, the son of Charles S. and Hattie M. Lightbody. He served in the U.S. Air Force as a 1st Lieutenant from 1943 to 1945. Dr. Lightbody was graduated from Colby College in 1948 and received his medical degree from the University of Maryland School of Medicine in 1952. Following his internship at the Worcester City Hospital from 1952 to 1954, Dr. Lightbody moved to Guilford where he practices General Medicine.



DR. LIGHTBODY



DR. MCAFEE



DR. BOSTWICK

He is a member of the Piscataquis County Medical Society, the Maine Medical Association, the American Medical Association, the American Academy of Family Physicians, and is Chairman of the Committee on Health Care Financing of the M.M.A. He is a Diplomate of the American Board of Family Physicians, and a member of the Board of Directors of Maine Blue Cross and Blue Shield.

Dr. Lightbody, his wife Margaret and two children, reside in Guilford.

DR. MCAFEE, of Portland, was born there on August 25, 1935, son of Harold G. and Elizabeth H. McAfee. Dr. McAfee was graduated from Deering High School in 1952, Bates College in 1956 and received his medical degree from Tufts University School of Medicine in 1960. He interned at the Maine Medical Center and served a residency in General Surgery from 1961 to 1965. Since 1965, Dr. McAfee has been attending surgeon at the Maine Medical Center and the Mercy Hospital, where he has been chief of surgery since 1974.

He is a member of the Cumberland County Medical Society, the Maine Medical Association, the American Medical Association, and is certified by the American Board of General Surgery. He is immediate Past President of the CCMS.

Dr. McAfee was formerly President of the American Cancer Society, Maine Division, Inc., Chairman of its Medical Affairs Committee and is currently a member of the National Board of Directors; was Chairman of the State Advisory Committee and State Ambulance Licensure Board of the Emergency Medical Services Division, Department of Health and Welfare; and is a long-time member of the Committee on Recruitment, Aid and Placement of the Maine Medical Association, serving as Chairman for several years.

Dr. McAfee served as Alternate Delegate to the AMA from 1972 to 1974 and has been Delegate to the AMA since 1974.

DR. DARLINGTON, of Augusta, was born in Olean, New York on January 7, 1922, son of J. Leon and Martha T. Darlington. He was graduated from Ohio University in 1943 and received his medical degree from State University of New York Upstate Medical Center, Syracuse in 1945. He interned at St. Luke's Hospital in Cleveland, Ohio and served a residency at the U.S. Marine Hospital in Staten Island. In 1952, he located in Augusta.

He is a member of the Kennebec County Medical Association, the Maine Medical Association, the American Medical Association, and is a member of the Liaison Committee Between the Maine Bar Association and the Maine Medical Association and the Committee on Membership of the M.M.A. He was chairman of the Legislative Committee for many years. Dr. Darlington was a former director of the National Tuberculosis Association, former President of the Maine Thoracic Society, the Maine Lung Association and the Maine Society of Internal Medicine.

Dr. Darlington has served as Alternate Delegate to the AMA since 1974.

# County Society Notes

## Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held on April 19, 1977. The meeting was called to order at The Ledges Inn, Wiscasset, Maine, at 8:35 p.m. by Vice-President, Dr. Aldo F. Llorente, with 25 members and guests present.

The minutes of the March meeting were read by the secretary and accepted as read.

There being no old business, Dr. David W. Schall discussed the interim session of the House of Delegates. Personnel will be needed at legislative hearings when Certificate of Need bills are discussed. A candidate for Assistant to the Executive Director of the M.M.A. was interviewed by the Executive Committee. The budget was discussed. The coming election for Executive Committee representative from this region was described and the contestants listed. A President and a President-elect of M.M.A. will have to be elected in June. A resolution will be introduced to enable M.M.A. past presidents to extend their tenure on the Executive Committee.

The membership instructed the delegates to use their best judgment in voting on these matters.

Dr. Richard C. Leck discussed the registered lobbyists for the M.M.A. and what they have done. He urged all members to continue to press their legislators to pass L.D. 727 *in toto*. The J.U.A., has been extended for two more years; most professional liability insurers will allow all physicians to join the J.U.A., at a considerable increase in premiums. He discussed the implications of various phrases embodied in proposed Certificate of Need legislation.

The meeting was adjourned at 9:50 p.m.

The regular monthly meeting was held at The Ledges Inn, Wiscasset, on Tuesday, May 17, 1977, with 43 members and guests present.

The meeting was called to order at 8:40 p.m. by the President, Dr. Anthony J. Horstman; the minutes of the last meeting were accepted as abstracted by the Secretary. There was no old or new business.

Dr. Morrison introduced Ms. Chris Bly and Mrs. Kitty Pfeiffer, who spoke on Safe Alternatives to Hospital Delivery-Room Childbirth. A lively discussion followed.

GEORGE W. BOSTWICK, M.D., *Secretary*

## Penobscot

The April meeting of the Penobscot County Medical Society was held on April 19, 1977 at the Red Lion Restaurant in Bangor, Maine. This was a combined meeting with the Penobscot County Bar Association. This combined meeting was the last in a series of three such combined meetings throughout the State with a presentation of a seminar on personal injury litigation. Doctors and lawyers from the five areas of Penobscot, Piscataquis, Hancock, Aroostook and Washington Counties had been invited. In view of the combined nature of the meeting and the presentation of a seminar, the business portion of the meeting was deferred to the May meeting. Following dinner, the President, Dr. John A. Woodcock introduced the panel of Dr. Hanbury of Belfast and Mr. Hazard and Mr. O'Leary of Portland law offices. We then proceeded with the panel discussion.

The response to the discussion was enthusiastic by both attorneys and doctors and plans for similar combined meetings in the future on other topics of mutual interest were considered.

The meeting was adjourned at 9:30 p.m.

H. CLEMENT JURGELEIT, M.D., *Secretary*

## Cumberland

The 412th meeting of the Cumberland County Medical Society was held at Valle's Steak House on April 21, 1977, with 66 members in attendance.

Applications for membership were read on Drs. George L. Pauk and Winthrop S. MacLaughlin.

Under old and new business, discussions were held on Health Career Awards, Metric Conversion Courses, Certificate of Need legislation and plans for the annual meeting.

A resolution was read on the death of Dr. Oscar R. Johnson by Dr. Carl A. Brinkman.

The program for the evening was the annual address from the President of the Maine Medical Association, Dr. Richard C. Leck. Dr. Leck, in his address, discussed budgetary matters and pending legislation which he described as part of "a flood of legislation" which will potentially have far reaching effects on the way in which we practice medicine. The address was well received and prompted a number of questions after which the meeting was adjourned at 9:15 p.m. by the President, Dr. Robert E. McAfee.

WESLEY J. ENGLISH, M.D., *Secretary*

## IATROGENIC ULNAR NERVE ENTRAPMENT AT THE ELBOW — *Continued from Page 332*

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# The Journal of the Maine Medical Association

Volume Sixty-eight

Brunswick, Maine, October 1977

Number 10

## Identification of the High Risk Mother and Fetus

HARRY W. BENNERT, JR., M.D., VERONICA DAVIS, C.N.M., M.S.  
and JOAN BENNERT, M. Ed.

A retrospective study was undertaken at the Maine Medical Center to test the ability of a scoring system to identify patients whose pregnancies and newborn babies will require close medical attention. The results of the study revealed that single 18 year old girls and young women less than 17 years of age contributed to a high risk group, not detected by the conventional scoring system. By the addition of these two categories to the Goodwin, Dunne and Thomas scoring system,<sup>3</sup> it became possible to enhance the ability of all trained personnel to identify high risk mothers and babies requiring intensive medical care.

In 1974, there were 15,100 live births to residents of the State of Maine. There were 244 infant deaths (children born alive who live 1 year or less) during this period and 190 were neonatal deaths (children born alive who live 28 days or less). It is estimated that the perinatal mortality rate of 1974 was 22.3 perinatal deaths (fetuses of 20 weeks or more gestation and through the first 28 days of life) per 1,000 live births.<sup>4</sup>

A high risk group can be defined and is well known to the obstetrician as those who have known medical problems such as diabetes mellitus, cardiac disease, hypertension; those with specific obstetrical problems such as multiple gestation or an incompetent cervix; those with known age risk factors such as those under seventeen and over thirty-five; and a group with miscellaneous problems. Seventy to eighty percent of perinatal mortality and morbidity can be found within a group of mothers that can be identified as high risk.<sup>1</sup>

### METHODS AND MATERIALS

The score card selected for this study was the

revised Nova Scotia Fetal Risk Project (NSFRP) score card<sup>7</sup> which utilizes the Goodwin, Dunne and Thomas scoring system<sup>3</sup> (see Figure 1 and 2). The records of 200 patients who were delivered between July 1975 and December 1976 were reviewed. One hundred of these patients had been seen in the High Risk Clinic at the Maine Medical Center. These patients had not been assigned to the high risk clinic by any scoring system, but on the basis of professional judgment. The remaining 100 were seen in the general prenatal clinic and were considered *not at high risk*.

Both groups were scored on their first visit, at 28 and 36 weeks gestation and also at their last visit using the NSFRP score card. Other risk factors not included by the NSFRP but noted in this study were single patients, those under 19 years of age, patients who smoked and drug abusers. These were recorded as comments on the back side of the score card (see Figure 2).

It is generally accepted<sup>8</sup> that infant mortality and morbidity can be substantially lowered by identifying the 20-30% of the obstetrical population that meet the criteria for high risk pregnancies. This paper describes the results of a study, undertaken at the Maine Medical Center to test the ability of a scoring system to identify the high risk mother.

The medical histories of the babies born to these 200 patients were traced in the records of the Neonatal Intensive Care Center (NICC). For the purpose of this study, all babies who died as well as those admitted to the intensive nursery were considered high risk.

### RESULTS

Of the 200 patients scored, sixteen babies ex-

**FIG. 1**  
**NOVA SCOTIA FETAL RISK PROJECT**  
**PRENATAL SCORE CARD**

PATIENT'S NAME \_\_\_\_\_ L.M.P. \_\_\_\_\_ E.D.C. \_\_\_\_\_

Doctor \_\_\_\_\_ Hospital \_\_\_\_\_ MSI # \_\_\_\_\_

PART A - Score 0,1,2 or 3 to a maximum of 3  
PART B - Score 0,1,2 or 3 to a maximum of 3  
PART C - Score 0,1,2,3 or 4 to a maximum of 4

A  
B  
+C

Fetal Risk Score

Check off all risk factors present (even if maximum score is reached) and tabulate the Fetal Risk Score and Gestation at each visit in the space provided below. (See Example)

<b>A BASELINE DATA</b> e.g. Age 35+ <input checked="" type="checkbox"/> 1 Age 35+ <input type="checkbox"/> 1 40+ <input type="checkbox"/> 2 Para 0 <input type="checkbox"/> 1 6+ <input type="checkbox"/> 2 Interval Less Than 2 Yrs <input type="checkbox"/> 1 Obesity 200 Lbs+ <input type="checkbox"/> 1 Diabetes Mild Moderate <input type="checkbox"/> 2 Severe <input type="checkbox"/> 3 Chronic Renal Disease with diminished Renal Function <input type="checkbox"/> 1 Pre-existing Hypertension <input type="checkbox"/> 3 140+ / 90+ <input type="checkbox"/> 1 160+ / 110+ <input type="checkbox"/> 2		<b>PREVIOUS OBSTETRICAL HISTORY</b> Abortion <input type="checkbox"/> Stillbirth <input type="checkbox"/> Neonatal Death <input type="checkbox"/> Surviving Premature Infant <input type="checkbox"/> Antepartum Hemorrhage <input type="checkbox"/> Toxemia <input type="checkbox"/> Mid-Forceps Delivery <input type="checkbox"/> Cesarean Section <input type="checkbox"/> Major Congenital Anomaly <input type="checkbox"/> Baby 10 Lbs+ <input type="checkbox"/> One Instance of Above <input type="checkbox"/> 1 Two or More Instances of Above <input type="checkbox"/> 2 RH Iso-immunized Mother <input type="checkbox"/> 2 + History of Erythroblastosis <input type="checkbox"/> 3	
<b>B PRESENT PREGNANCY</b> e.g. Hydramnios <input checked="" type="checkbox"/> 3 Bleeding, Before 20 Weeks Alone <input type="checkbox"/> 1 With Pain <input type="checkbox"/> 2 Bleeding, After 20 Weeks Ceased <input type="checkbox"/> 1 Continues <input type="checkbox"/> 2 With Pain <input type="checkbox"/> 3 With Hypotension <input type="checkbox"/> 3 Spontaneous Premature Rupture of Membranes Latent Period 24 Hr+ <input type="checkbox"/> 1 <input type="checkbox"/> 2 Anemia 8 to 10 gms <input type="checkbox"/> 1 Less than 8 gms <input type="checkbox"/> 2 No Prenatal Care <input type="checkbox"/> 2 1 to 3 Prenatal Visits <input type="checkbox"/> 1		Toxemia Mild Moderate <input type="checkbox"/> 1 Severe <input type="checkbox"/> 3 Hydramnios (Single Fetus) <input type="checkbox"/> 3 Multiple Pregnancy <input type="checkbox"/> 2 Abnormal Glucose Tolerance <input type="checkbox"/> 1 Decreasing Insulin Requirement <input type="checkbox"/> 3 Maternal Diabetic Acidosis <input type="checkbox"/> 3 Maternal Pyrexia <input type="checkbox"/> 1 Pyrexia + FHR Greater than 160 <input type="checkbox"/> 2 RH Negative <input type="checkbox"/> With Antibody Titre <input type="checkbox"/> 2 With Amniotic Fluid Liley Zone 111 <input type="checkbox"/> 3	
<b>C GESTATIONAL AGE (at time of scoring)</b> e.g. 29 - 32 Wks <input checked="" type="checkbox"/> 3 28 Wks or under <input type="checkbox"/> 4 29-32 Wks <input type="checkbox"/> 3 33-35 Wks <input type="checkbox"/> 2		36-37 Wks <input type="checkbox"/> 1 38-41 Wks <input type="checkbox"/> 0 42 Wks <input type="checkbox"/> 1 43 Wks OR More <input type="checkbox"/> 2	
<b>PRENATAL VISITS (GOOOWIN, DUNNE AND THOMAS FETAL RISK SCORING SYSTEM)</b>			
e.g. Jan. 2/74		DATE	
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	
25		26	
27		28	
29		30	
31		32	
33		34	
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75		76	
77		78	
79		80	
81		82	
83		84	
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	
97		98	
99		100	

DELIVERY DATE \_\_\_\_\_ GESTATION \_\_\_\_\_ /40 FINAL FETAL RISK SCORE \_\_\_\_\_ /10  
(= The Fetal Risk Score Just Prior To Labour)

The score card is utilized in the following manner: At each visit, the patient is evaluated and the risk factors checked. Section A and B could each total a maximum of 3 points; Section C, 4 points. The total of Section A, B and C was recorded with the date of the visit and gestational age in the appropriate boxes. A patient whose score was 7 or more on the first visit was considered high risk. Any patient, on subsequent visits whose score did not decrease as the pregnancy progressed, was considered at high risk.

hibited serious pathology at birth. Three were stillborns, one set of twins died shortly after birth, and 11 were admitted to NICC.

Originally, the 200 patients were subjectively grouped into high risk and *not at high risk* by professionals. The 100 high risk patients gave birth to twelve babies exhibiting serious pathology; 2 stillborns, the set of twins, and 8 NICC babies (see Table 1).

Using the NSFRP score card, the patients were divided into high risk and *not at high risk* groups. Of the 200 patients, only 23 mothers were identified as high risk on their first visit. An additional 16 were added during the course of their pregnancies. These 39 high risk mothers identified by the score card gave birth to 2 stillborns, the twins and 6 NICC babies or 10 infants were identified as exhibiting (potentially) serious pathology at birth (see Table 2).

PATIENT'S NAME \_\_\_\_\_ L.M.P. \_\_\_\_\_ E.D.C. \_\_\_\_\_

Doctor \_\_\_\_\_ Hospital \_\_\_\_\_ MSI # \_\_\_\_\_

DISCHARGE SUMMARY MAY BE COMPLETED AT OFFICE OR HOSPITAL

DELIVERY DATE \_\_\_\_\_ GESTATION \_\_\_\_\_ /40 FINAL FETAL RISK SCORE \_\_\_\_\_ /10  
(= The Fetal Risk Score Just Prior To Labour)

LABOUR: Normal ☐ Abnormal ☐

DELIVERY: Spontaneous ☐ Forceps ☐ C-Section ☐ BREECH ☐

NEWBORN: Male ☐ Female ☐ Weight – gms \_\_\_\_\_ OR lbs-oz \_\_\_\_\_

Approximate Apgar Score @ 1 min., /10, @ 5 min., /10

OUTCOME: Abortion ☐ Stillborn ☐ Lived ☐ Neonatal Death ☐  
Date of Neonatal Death \_\_\_\_\_

COMMENTS (PRN) Re ANTEPARTUM, INTRAPARTUM AND NEWBORN PERIODS:

During the evaluation of the scores, it appeared that 61 of the high risk pregnancies identified by the professionals went undetected when using the NSFRP score card. The two major risk factors omitted in the scoring system, but included in the professional evaluation were the patients who were 17 years old or younger and the patient who was 18 years old and single. Therefore, it is necessary to add two additional categories to Section A of Figure 1 (Baseline Data).<sup>\*</sup> The maximum score for Section A remains at 3.

## BASELINE DATA

Age 17 or less .....	2*
18 and single .....	1*
35+ .....	1
40+ .....	2

Of the 200 patients reviewed with the two additions, seventy were identified as high risk and 9 were added during the course of their pregnancy. These

TABLE 1

**NOT AT HIGH RISK\***

High Risk Babies	first visit score	28 wk score	36 wk score	last visit score	Comments
Stillborn #1	5	5	2	2	Toxemia, fetal dist., 19 YO
NICU BABY #1	5	5			39 wk gest., 1.5 kg., 17 YO
NICU BABY #2	4				36 wk gest., 1.8kg., 3 clinic visits
NICU BABY #3	7	9			28 wk gest., 1.25kg.
					Total: 96 patients + 4 spont. abortions
<b>HIGH RISK*</b>					
Stillborn #2	7				31 wk gest., IUFD, 18 YO, one clinic visit
Stillborn #3	8	8			24 wk gest., revised del. date
Neonatal death of twins	6	9			RDS
NICU BABY #4	5	8			27 wk gest., fetal dist., abrupt. placent. .952kg. 17 YO
NICU BABY #5	5	5	6		32 wk gest., 1.8kg., 19 YO, chronic drug abuser
NICU BABY #6	5	5	5		33 wk gest., C-sec., 15 YO, 1.9kg.
NICU BABY #7	5	4	2	5	Severe toxemia, C-sec., 1.34kg.
NICU BABY #8	5	5	1		36 wk gest., multiple anomalies
NICU BABY #9	5	4	1	1	respiratory arrest, 16 YO
NICU BABY #10	4	6	3		placent. previa., 1.25kg., drug abuser
NICU BABY #11	7	6	4	3	40 wk gest., 18 YO
					Total: 100 patients

\*Based on professional judgment

women gave birth to 2 stillborns, 1 set of twins and 9 babies that were sent to the NICU or 13 infants exhibiting pathology at birth (see Table 3). A group of 126 *not* identified as high risk after the inclusion of the new categories, gave birth to one stillborn (not recognized until delivery), a baby with multiple congenital anomalies and a premature baby whose mother had been scored only three times prenatally.<sup>†</sup>

### DISCUSSION

In the retrospective review of the charts of 200 patients assigned by professional judgment alone to either a general prenatal clinic or a high risk clinic, it can be seen that patients assigned to high risk clinic gave birth to 12 of the 16 high risk infants (see Table 1). The data confirms that clinical judgment by obstetricians aware of risk factors can identify high risk mothers. This retrospective study was designed to test the ability of a scoring system to assist in the identification of the high risk mother by *all* persons providing prenatal care.

As shown in Table 2, the Goodwin, Dunne and Thomas scoring system as used in the Nova Scotia Fetal Risk Project identified 10 of the 16 high risk babies. On the basis of an initial score of 7, the score card picked out only 39 of the 100 mothers identified by the professional as high risk. Nine out of the 39 patients delivered high risk babies, five of which were not identified until late in their pregnancies. This does not allow the professional time to attempt to correct or modify the disorder believed to be the basis of the high risk state.

<sup>†</sup>Four spontaneous abortions were not included in the high risk group statistics because data reviewed for the high risk patient was prospective in contrast to the *not at high risk* group whose records were reviewed retrospectively, having been identified in the records of the delivery room.

TABLE 2

**NOT AT HIGH RISK\***

High Risk Babies	first visit score	28 wk score	36 wk score	last visit score
Stillborn #1	5	5	2	2
NICU BABY #1	5	5		
NICU BABY #2	4			
NICU BABY #6	5	5	5	
NICU BABY #8	5	5	1	
NICU BABY #9	5	4	1	1
Total: 161 patients				

**HIGH RISK\***

Stillborn #2	7			
Stillborn #3	8	8		
Neonatal death of twins	6	9		
NICU BABY #3	7	9		
NICU BABY #4	5	8		
NICU BABY #5	5	5	6	
NICU BABY #7	5	4	2	5
NICU BABY #10	4	6	3	
NICU BABY #11	7	6	4	3
Total: 35 patients + 4 spontaneous abortions				

\*Based on the score card used by the Nova Scotia Fetal Risk Project

In reviewing the differences in risk score factors as used by the score card vs. professional judgment, it was evident that the teenager (17 years or less) and the single eighteen year old were groups not identified by the NSFRP score card. A study by Chase<sup>2</sup> showed that the perinatal mortality rates for young (18 or less) as well as older mothers (35+) are unacceptably high. The baby of the young mother is at greatest risk for neonatal mortality. Other studies<sup>1,2,6,8,10</sup> vary as to the definition of the risk factors, but they all agree that the teenager and her baby are at risk.

With the revision to include the teenager (17 or less) and single eighteen year old categories, the

TABLE 3

<i>NOT AT HIGH RISK*</i>				
High Risk Babies	first visit score	28 wk score	36 wk score	last visit score
Stillborn #1	5	5	2	2
NICU BABY #2	4			
NICU BABY #8	5	5	1	
Total: 126 patients				
<i>HIGH RISK*</i>				
Stillborn #2	8			
Stillborn #3	8	8		
Neonatal death of twins	6	9		added during pregnancy
NICU BABY #1	7	7		
NICU BABY #3	7	9		
NICU BABY #4	7	10		
NICU BABY #5	5	5	6	added during pregnancy
NICU BABY #6	7	7	7	
NICU BABY #7	5	4	2	5 added during pregnancy
NICU BABY #9	7	6	3	3
NICU BABY #10	4	6	3	added during pregnancy
NICU BABY #11	7	6	4	3
Total: 70 patients + 4 spontaneous abortions				

\*Based on author's revision of Nova Scotia Fetal Risk Project Score Card.

score card was then able to identify 74 of the high risk mothers and 13 of the 16 high risk babies (see Table 3). Professional judgment without the score card identified 12 of the 16 high risk babies (see Table 1).

In addition to its predictive value, the score card is concise and easy to use. As the patient receives a score at each prenatal visit, there is continual updating of the patient's risk status during her pregnancy. To improve the ability to follow the newborns, it is suggested that the infant's name and hospital number be recorded on the mother's risk evaluation card.

With more midwives, physician assistants, and nurse practitioners becoming involved in prenatal care, a scoring system such as developed by Goodwin, Dunne and Thomas, as modified by the Nova Scotia Fetal Risk Project, and further expanded by this study, enhances the ability of *all* professionals to identify a high risk pregnancy. It is hoped that a prospective study will be undertaken in Maine with the objective of integrating this score card into the permanent record of each prenatal patient. Persons interested in participating in this prospective study may contact Harry W. Bennert, Jr., M.D., 47 Bramhall Street, Portland, Maine 04102.

#### ACKNOWLEDGMENT

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# Staging and Therapy of Multiple Myeloma

DELVYN C. CASE, JR., M.D.\*

Multiple myeloma is a malignant proliferation of a clone of B-lymphocytes (bone marrow derived, or bursa-equivalent cells), producing a monoclonal gammopathy in the serum and/or urine. These cells are derived from malignant transformation of lymphoid cells in the medullary or secretory area of the lymph node.<sup>1</sup> The infiltration of malignant plasma cells in the bone marrow and other tissues and the abnormal expansion of globulins produce the clinical symptomatology and laboratory manifestations (Table 1).

The use of melphalan and prednisone in myeloma has significantly prolonged survival and quality of survival in the majority of patients treated.<sup>2</sup> Bone disease, anemia, hypercalcemia, and renal failure have all been ameliorated by the cyclical administration (every 6 weeks) of these drugs.

Developments in staging and drug therapy have provided further advancements in the care of these patients. Quantitation of the synthesis of myeloma proteins and the relationship of clinical and laboratory findings to the myeloma cell mass have been shown to be of prognostic value in the evaluation and treatment of patients.

The development of the staging system for myeloma has been the work of Salmon, et al. This system was first based upon metabolic studies designed to calculate the myeloma cell mass.<sup>3</sup> Serial estimations of tumor cell mass and tumor regression were determined by calculating the total protein secreted and the synthesis of protein by individual myeloma cells. A mathematical equation was then developed that could estimate with a high degree of confidence the globulin synthetic rate and tumor cell number.<sup>4</sup> The number of myeloma cells per square meter of body surface area in clinically detectable disease is usually within the range  $<0.6 - >1.2 \times 10^{12}$  cells/m<sup>2</sup>. A clinical staging system for myeloma has evolved after the recognition that certain clinical and laboratory parameters were directly related to the estimated tumor cell mass: hemoglobin, serum calcium level, M-component ("myeloma protein level") in the serum and/or urine, and extent of bone disease<sup>5,6</sup> (Table 2).

Patients with low measured myeloma cell mass were found to have a normal or only slightly depressed hemoglobin, normal calcium level, normal bone structure or a solitary plasmacytoma, and low levels of M-component production. Survival in this group is  $>12$  years (Table 3).

Stage II represents an intermediate group with a median survival of 4 and one-half years. The clinical

TABLE 1

## CLINICAL AND LABORATORY CHARACTERISTICS OF MYELOMA

Weakness and lethargy
Bone pain
Cold sensitivity
Lytic bone disease
Susceptibility to infection
Neurologic manifestations (peripheral neuropathy)
Anemia
Leukopenia
Thrombocytopenia
Bone marrow infiltration by plasma cells
Monoclonal gammopathy in serum and/or urine
Coagulation abnormalities
Hypercalcemia
Renal dysfunction
Amyloidosis

TABLE 2

## MYELOMA STAGING SYSTEM\*

Stage	Clinical Staging System Criteria	Measured myeloma cell mass (cells $\times 10^{12}/m^2$ )
I	All of the following: 1. Hemoglobin value $>10g/100ml$ 2. Serum calcium value normal ( $\geq 12mg/100ml$ ) 3. On roentgenogram, normal bone structure (scale 0) of solitary bone plasmacytoma only 4. Low M-component production rates a. IgG value $< 5g/100ml$ b. IgA value $< 3g/100ml$ c. Urine light chain M-component on electrophoresis $< 4g/24$ hours	$<0.600$    (Low)
II	Fitting neither Stage I nor Stage III	0.600 - 1.200 (Intermediate)
III	One or more of the following: 1. Hemoglobin value $< 8.5g/100ml$ 2. Serum calcium value $> 12 mg/100ml$ 3. Advanced lytic bone lesions (scale 3) 4. High M-component production rates a. IgG value $> 7g/100ml$ b. IgA value $> 5g/100ml$ c. Urine light chain M-component on electrophoresis $> 12 g/24$ hours	$>1.200$   (High)

\*After Durie and Salmon<sup>6</sup>

characteristics of this group fit a measured cell mass of  $0.6 - 1.2 \times 10^{12}$  cells/m<sup>2</sup>.

Patients in Stage III have the worst prognosis with a median survival of 2 years despite therapy. In this group, patients have the highest cell mass,  $>1.2 \times 10^{12}$  cells/m<sup>2</sup>. This high cell mass, with high levels of protein, produces severe clinical disease with anemia, and/or hypercalcemia, and/or advanced lytic bone destruction. Any one of these three clinical/laboratory determinants is a poor prognos-

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TABLE 3

## SURVIVAL BY STAGE IN MYELOMA\*

Stage	Median Survival
I	> 12 years
II	4½ years
III	2 years

\*After Durie and Salmon<sup>6</sup>

tic sign placing the patient in the most advanced stage.

An understanding of staging and the implications for survival allow for a rational approach to therapy. Patients with Stage I disease (Table 3) have a median life expectancy of >12 years. Often these cases present with clinical symptoms after years of asymptomatic protein "spikes", undiagnosed bone disease, persistently elevated sedimentation rate, or rouleau formation. Untreated, the disease process would progress with major clinical complications. Therapy, however, might produce excessive morbidity and/or lead to premature mortality through the induction of acute leukemia, occasionally seen in patients receiving long-term treatment for myeloma.<sup>7,8</sup> Therapy with the standard regimen of melphalan and prednisone,<sup>2</sup> with consideration of discontinuing therapy after a remission is achieved, is a logical approach.

More commonly (>80% in one series)<sup>9</sup> patients present in Stages II and III. Life expectancy is rather limited (Table 3). The combination of melphalan and prednisone achieves remissions in 50% of patients with a median survival of 2 years.<sup>2</sup> Earlier studies combining melphalan and prednisone with other drugs (especially procarbazine and vincristine) were unsuccessful in producing higher remission rates or extending survival.<sup>10</sup> Recently a 5-drug regimen consisting of melphalan, prednisone, cyclophosphamide, vincristine, and B.C.N.U. (1,3-bis (2-chloro-ethyl)-1-nitrosourea) (an experimental drug requiring informed consent) has been reported<sup>11</sup> and updated.<sup>12</sup> Results after 3 years of study predict that remission duration will be extended to 36 months and survival extended to >48 months. Importantly, the response in the previously untreated patients has been improved from 50% (achieved with melphalan and prednisone) to 90%. In addition, 50% of patients who have failed to respond to melphalan and prednisone or who have relapsed during therapy with these drugs have been found to respond to this 5-drug combination.

Despite significant advances in therapy, all patients with myeloma eventually relapse. Repeated determinations of the myeloma cell mass suggest that only a one log kill is achieved with various drug combinations. This corresponds to a 90% tumor cell

kill. Although reduction of the tumor mass from  $10^{12}$  cells/m<sup>2</sup> to  $10^{11}$  cells/m<sup>2</sup> produces significant clinical and laboratory improvement, substantial myeloma persists. After a period of time in remission, the cell mass rises as the tumor cells become resistant to the particular regimen of drugs, or as a small population of originally drug-resistant cells continue to proliferate despite remission or elimination of the drug-sensitive clone.<sup>13</sup> The current strategy is to add other drugs during the remission phase in an attempt to achieve a greater log kill of tumor cells. Early attempts have been unsuccessful.<sup>9</sup>

Significant progress in the therapy of myeloma has been achieved. In the pre-melphalan era, survival was 13 months.<sup>14</sup> With melphalan and prednisone, survival has been prolonged to 24 months. With the 5-drug regimen, survival is greater than 48 months. These treatment regimens can best be evaluated and applied by careful staging of patients and appreciating the implications of staging upon survival.

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# Two Late Complications of Laparoscopic Tubal Ligation

JAMES W. GEORGITIS, M.D.\*

Laparoscopic tubal ligation by fulguration has become the most common form of elective sterilization. Recognized complication of hemorrhage, inadvertent burns of bowel or abdominal wall, gas embolization, bowel or gastric insufflation and acute salpingitis are well known. Late complications of adhesion formation, sterilization failure, menstrual irregularity, and herniation through trocar sites are also well documented.<sup>3</sup> To this list must be added yet two more late complications, repeat ectopic pregnancy and twisted pyosalpinx.

## CASE REPORTS

### CASE #1

A 33-year-old white female gravida IV, para II, Ab I presented with right lower quadrant pain of 4 hours' duration associated with breast tenderness and (+) HCG. Her last menstrual period was 3 months prior to admission. Past history included laparoscopic tubal ligation by triple burn technique followed by a 4-year asymptomatic interval. One year prior to admission pelvic pain was treated with an antibiotic for a diagnosis of PID. This failed to resolve and an ovarian cyst was diagnosed. At laparoscopy a tubal pregnancy was noted and laparotomy revealed adequate fulguration and separation of both uterine tubes. A unilateral salpingo-oophorectomy was performed. Her current physical exam revealed another adnexal mass of 6 cm on the right side. Culdocentesis was positive for gross blood and at laparotomy a repeat ectopic pregnancy was found in the distal tube segment in an adequately fulgurated and divided uterine tube. No tubal patency or tubal reanastomosis was visualized on the mesentery connecting the tube segments.

### CASE #2

A 32-year-old white female gravida IV, para IV presented with the acute onset of nausea, vomiting, right upper and lower quadrant pain with right anterior thigh radiation. A tentative diagnosis of acute cholecystitis was made and evaluation undertaken. IV cholangiography, IVP, upper GI series, and barium enema were all normal with the exception of a vague impression of a right lower quadrant mass on barium enema fluoroscopy. Gynecological consultation revealed the uterus to be retroflexed, a poorly defined right adnexal mass present, and culdocentesis productive of translucent yellow fluid with a sterile growth and protein content of 951 mg%. CBC, urine analysis, SMA 12 were all normal except for a sedimentation rate elevated to 51 mm/hr. Past history revealed laparoscopic tubal ligation by tubal cauterization and segmental resection technique three years prior to admission. Evaluation under anesthesia, laparoscopy and laparotomy revealed a twisted pyosalpinx of the distal tube segment. Right salpingo-oophorectomy was performed.

Repeat ectopic pregnancy and twisted pyosalpinx have not previously been reported as late complication of laparoscopic tubal ligation. An ectopic pregnancy is itself a rare event in the sterilized population occurring .6% of the time. The incidence of

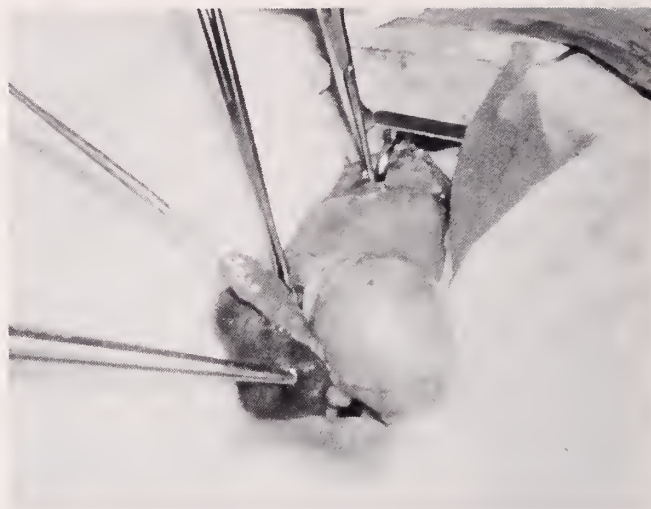


Fig. 1. Uterus and remaining fallopian tube with ectopic pregnancy (Case #1).



Fig. 2. Pyosalpinx in laparoscopic dissected uterine tube (Case #2).

ectopic pregnancy following laparoscopic tubal sterilization is reported as 0.07%.<sup>4</sup> Ectopic pregnancies are still a serious problem and account for 6.5% of maternal mortality in the United States.

Most ectopic pregnancies present with vaginal bleeding followed by onset of abdominal pain (42.8%). Pain alone occurred in 22.4% of cases. Bleeding and pain together were present in 71.4%. Amenorrhea is not diagnostic and occurred in only 34.7%. The average number of days from menses

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until removal of ectopic pregnancy was 58 days. 16.3% of patients usually give a history of previous pelvic infection, however, laparotomy obtained histological tubal sections have shown previous infection in 53.5%. Sixty-nine percent of all ectopic pregnancy patients are seen prior to surgery by a physician who makes an incorrect diagnosis.<sup>5</sup>

The failure rates of sterilization as reviewed by Garb in a series of 29,496 tubal procedures revealed the highest failure rate following cornual excision (2%). Pomroy's procedure was lower with a failure rate of 0.25% and laparoscopic tubal sterilization was least with a failure rate of 0.07%. Ectopic presentation as a failure of sterilization was present in .6% of sterilized patients.<sup>6</sup>

Ectopic pregnancy occurrence following laparoscopic sterilization has been attributed to incomplete cauterization, tubal reanastomosis, and recornualization with pin point patency. Hysterosalpingography attempting to demonstrate this has only succeeded in showing that cauterized uterine tubes could be "blown open" by hysterosalpingography 6 weeks post cauterization and did not confirm the presence of reanastomosis.

In case number 1, a pin point area must have permitted egress of sperm from the uterine cavity and implantation of a fertilized ovum into the fimbriated end of the cauterized tube. No evidence of this opening or recornualization, or tube reapproximation was evident at two laparotomy procedures but must have been present prior to the first ectopic pregnancy.

Case number 2 demonstrates that tubal dessication creates new anatomical relationships. The distal tube and fimbria are now unsupported by attachment to the uterus at one end. Suspended by a mesentery they may undergo torsion. The previous open tube is now a blind end pouch which, if inflammatory changes occur at the fimbria end, may be converted into a sealed viscus (hydrosalpinx).

Theoretical consideration to avoid such late

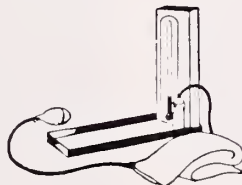
laparoscopic tubal ligation complication would be avoidance of this procedure in individuals with previous PID which may predispose to hydrosalpinx. Far more important however, is to consider different diagnostic possibilities in a patient previously sterilized by laparoscopy. Assumptions of impossibilities of hydrosalpinx, torsion of tubes, or ectopic pregnancy may lead to diagnostic error. Any procedure creating new anatomical relationship will predispose to new presentation of surgical disease. An awareness of these possibilities should influence surgical evaluation of the acute abdomen in a laparoscopic sterilized patient.

## SUMMARY

Two previously unreported complications of late onset following laparoscopic tubal ligation (repeat ectopic pregnancy and twisted pyosalpinx) are discussed.

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# Free Perforation of the Jejunum in Crohn's Disease

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Acute free perforation of the bowel is a rare occurrence in patients with granulomatous enteritis. Since the disease was first described by Crohn in 1932,<sup>1</sup> only forty-two instances of perforation have been reported. Among these only five cases of jejunal perforation have been noted. Because of its rarity and the implications concerning treatment, the following case is presented.

## CASE REPORT

J. P., a 21-year-old male, entered the emergency room of the MMC with a two-hour history of sudden and severe generalized abdominal pain. The onset of pain followed a light meal and increased in intensity until the time of admission. The pain was neither aggravated nor lessened by position or movement. During the year prior to admission, the patient had vague symptoms of indigestion relieved by food and antacids. In his past history there were no previous complaints of severe abdominal cramps, bloody diarrhea, weight loss, fever, or hematemesis. A barium study of the upper GI tract one year prior to admission had revealed considerable irritability and spasm of the duodenal bulb but no identifiable ulcerations were seen. The family history was negative for ulcerative colitis, Crohn's disease or joint disease. The father had a history of peptic ulcer disease.

There was diffuse abdominal guarding and rebound tenderness on examination of the abdomen. The bowel sounds were absent. The stool was guaiac negative. Temperature was elevated to 39 and the pulse rate was 110/minute. Laboratory studies revealed a leukocyte count of 18,000 with a marked shift to the left. The hematocrit was 41.3%. The liver function tests, except for an SGOT level of 85 units, and the Serum amylase levels were normal.

Supine abdominal x-rays showed no signs of distention or obstruction but the upright abdominal films demonstrated free air beneath both leaves of the diaphragm. A laparotomy was promptly performed with a tentative diagnosis of a perforated peptic ulcer. Upon exploration of the peritoneal cavity 500 cc's of serosanguinous fluid was found along with a twenty centimeter segment of hyperemic inflamed proximal jejunum. A 1.0 centimeter perforation of the jejunal wall along the mesenteric border was identified. Seventy-five centimeters of jejunum was excised and an end-to-end anastomosis was performed linking jejunum to ileum. The proximal segment of the specimen was markedly narrowed with the lumen almost totally obstructed by a thickened and edematous mucosal wall.

Postoperatively the patient had daily temperature elevations to 40.5, and a liver-lung scan five days later demonstrated medial displacement of the liver. Subsequently, a Gallium scan on the thirteenth post-op day showed an increased uptake in the sub-hepatic space. The next day a sub-diaphragmatic abscess was drained, and temperature returned to normal. One month after admission the patient was discharged on a bland diet without specific medications.

The operation specimen showed marked edema and both a leukocytic and lymphocytic infiltrate extending from the mucosa to the muscularis. There was focal granulomatous disease at the site of the perforation, and focal ulceration with several ulcer

craters deeply penetrating the wall of the bowel. Epithelioid granulomata were seen in the submucosa and muscularis of the bowel.

## DISCUSSION

Perforation of the small bowel in association with regional enteritis was described by Crohn several years after the disease was first described. He noted that perforation of the terminal ileum was rare, occurring most often when the disease had been present for a long time. Crohn, speculating as to the rarity of perforation thirty-five years later commented, "That acute perforation can and does occur in the presence of diffuse suppurative infiltration of the mucosa, submucosa and muscularis is because the protective granulomatous reaction has not yet taken place."<sup>2</sup> The protective granulomatous reaction is the hallmark of regional enteritis. It is composed of collections of lymphoid tissue with germinal centers throughout all three layers of the intestinal wall. These foci develop ulcerations and subsequently intramural abscess formation takes place. This may initiate fistula formation. The process may continue leading to fistulous tracts to surrounding bowel segments or other abdominal organs, or it may become quiescent and develop granulomatous tissue in adjacent mesentery. Coarse, gross thickening of the bowel wall ensues. These protective mechanisms evolve over a variable time period and perforation usually does not occur. If the inflammatory process is rapidly progressive and if the channel of infiltrating tissue rapidly spreads throughout the layers of the bowel wall a perforation could result. Other investigators have felt that edema of the inflamed bowel segment may cause obstruction, and induce perforation.<sup>3</sup> In a review of forty-two reported cases of perforated regional enteritis by Nasr, et al.,<sup>4</sup> in 1969, less than half presented with an acute process with no previous history of the disease. The majority of perforations occurred in the ileum, ten were found in the large colon, and five cases involved a segment of jejunum. Of the jejunal perforations, only one presented with an acute episode.

There has been an increased incidence of regional enteritis in the past ten years. Whether this is due to more definitive means of identification, such as endoscopic small bowel biopsies, or merely an increased awareness by physicians is unknown. All portions of the gastrointestinal tract including duodenum and stomach have been reported to be

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# The Case for Adjuvant Radiotherapy in Adenocarcinoma of the Rectum

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Rectal carcinoma is the fifth most common neoplasm in the United States. Its incidence is exceeded by carcinomas of the lung, breast, remainder of the colon, and the prostate. Approximately 31,000 Americans will be stricken by this disease in 1977.

Since the introduction of the Miles abdominoperineal (AP) resection in 1908,<sup>1</sup> no major therapeutic advance has occurred which has significantly influenced local recurrence. In the last three years several papers<sup>2-7</sup> have reported the beneficial use of adjuvant radiotherapy in conjunction with an AP resection. The present study was instituted to evaluate the failure rate following AP resection for adenocarcinoma of the rectum and the effect of local failure on the quality of survival.

## PATIENTS AND METHODS

Using the tumor registry and record room files at the Maine Medical Center and Mercy Hospital, both in Portland, Maine, the efficacy of abdominoperineal (AP) resections performed for adenocarcinoma of the rectum or rectosigmoid was evaluated. One hundred and seven patients had this procedure at the Maine Medical Center between 1963 and 1974. Thirty-one patients had this operation at Mercy Hospital between 1960 and 1974. All patients were followed for a minimum of two years, and no patients were lost to follow up for that time period. No patients received adjuvant radiotherapy or chemotherapy in this series. The following 16 cases were deleted from the study: nine patients died within three months of operation without tumor, five patients with concomitant tumors (two bronchogenic and one each of breast, hypernephroma, and histiocytic lymphoma), and two patients with liver involvement at time of AP resection.

Included in this series were five patients that had recurrence from previous anterior sigmoid resections. An additional seven patients, who were included, underwent an AP resection with tumor adherent to the pelvic sidewall in four, positive histological margin in two, and one patient with an undiagnosed lung nodule that was eventually found to be metastasis. The inclusion of these 12 patients did reduce the five-year survival data, but did not significantly alter either the failure rate by stage or the data on location of tumor failures.

On the basis of operative notes and pathology reports of the 122 study cases, each tumor was

categorized as involving the mucosa alone, involving the submucosa and muscle of the wall, penetrating through the muscle but remaining within the serosa (when present), penetrating through the serosa or through the muscularis when serosa is not present, and presence or absence of involved nodes. In case of doubt, the original slides were reviewed and staged.

The staging system used to analyze our data is from Astler and Collier,<sup>8</sup> as modified by Gunderson and Sosin,<sup>9</sup> which is as follows:

"A-lesion limited to the mucosa, nodes negative; B<sub>1</sub>-extension of lesion through mucosa but still within the bowel wall, nodes negative; B<sub>2</sub>-extension through the entire bowel wall with or without invasion of surrounding tissue or organs, nodes negative; C<sub>1</sub>-positive lymph nodes but lesion limited to bowel wall; C<sub>2</sub>-positive lymph nodes and lesion through the entire bowel wall."<sup>9</sup>

Astler-Collier's staging system separates B<sub>1</sub> and B<sub>2</sub> on the basis of penetration through the muscle, while Gunderson-Sosin use penetration of the full thickness of the wall to demarcate these two stages. Recent data<sup>9,10</sup> indicates that the latter is a more important prognostic sign.

The use of this modified system allows comparison with published results using the Dukes' classification. Dukes A includes Stages A and B<sub>1</sub>, Dukes B equals Stage B<sub>2</sub>, and Dukes C includes both Stages C<sub>1</sub> and C<sub>2</sub>.

In evaluating the location of symptomatic failures, only those recrudescences of cancer that caused symptoms were counted. Patients with pelvic pain and asymptomatic lung nodules were considered to have local symptoms only. On the other hand, one patient with symptoms of distant metastases had asymptomatic perineal nodules and was considered as having distant metastases only.

Diagnosis of tumor failure was made by biopsy in many cases. However, in some cases, this was established on the basis of physical findings, abnormal radiologic procedures, and/or abnormal blood chemistry tests, including liver function test.

## RESULTS

### *Tumor Failure Rate vs. Depth of Penetration*

Penetration of the full thickness of the rectal wall was found to be the best indicator of risk of tumor failure. As shown in Table 1, B<sub>1</sub> and C<sub>1</sub> lesions had failure rates of 16.7% and 20% respectively. When the wall was penetrated, then 18 of 37 patients or 51.4% had tumor recrudescence when nodes were

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TABLE 1

DEPTH OF PENETRATION VS. FAILURE			
Stage	NED*	Failure	% Failure
A	1	0	0
B <sub>1</sub>	35	7	16.7%
B <sub>2</sub>	18	19	51.4%
C <sub>1</sub>	4	1	20 %
C <sub>2</sub>	8	29	78.4%
Total	66	56	45.9%

\*No evidence of disease

TABLE 2

NUMBER OF INVOLVED NODES VS. FAILURE		
Number of Nodes Involved	NED*	Failure
1	6	6
2	2	8
3	2	3
4 or more	2	10
Not stated	0	3
Total	12	30

\*No evidence of disease

negative (B<sub>2</sub>), and 29 of 37 patients or 78.4% had failed when nodes were positive (C<sub>2</sub>). The failure rates for patients with negative nodes was 32.5%, while it was 71.4% for the 42 patients with positive nodes.

Of the four patients whose tumor penetrated through the muscle, but was within the confines of the wall, only one had tumor failure. These patients would be considered as Stage B<sub>2</sub> by the Astler-Coller system but are included in the Stage B<sub>1</sub> by Gunderson-Sosin's modification.

#### Failure Rate vs. Number of Positive Nodes

Table 2 indicates that 6 of the 12 patients with positive nodes that did not fail had only one node involved. However, the presence of one positive node was still associated with a 50% risk of failure. The presence of two or more nodes involved with tumor was a poor prognostic sign, since 21 of 27 or 77.8% had failure.

#### Failure Rate vs. Grade of Tumor

Although other studies have indicated a correlation of grade of histology with risk of failure, no association was found in our series (Table 3). In Table 4, a trend is suggested that Stages B<sub>1</sub> and B<sub>2</sub> tend to have Grade 2 tumors while Stage C has more Grade 3 lesions.

#### Location of Symptomatic Failure

A total of 56 patients had recrudescence of tumor, which is 45.9% of the 122 evaluable patients. The patterns of failure were divided into five categories as shown in Table 5.

The first includes those who had symptoms of local pelvic failure without symptoms of distant metastases up to the time of their demise. Some of

TABLE 3

HISTOLOGICAL GRADE VS. FAILURE		
Grade	NED*	Failure
I	3	4
II	36	24
III	22	20
Not stated	5	8
Total	66	56

\*No evidence of disease

TABLE 4

HISTOLOGICAL GRADE VS. STAGE					
Grade	A	B <sub>1</sub>	B <sub>2</sub>	C <sub>1</sub>	C <sub>2</sub>
I	0	4	1	0	2
II	1	24	21	2	12
III	0	9	13	2	18
Not stated	0	5	2	1	5
Total	1	42	37	5	37

these patients had asymptomatic pulmonary or hepatic nodules. Thirty-two of the 56 patients who had tumor failure (57.2%) were included in this category. The average duration of symptoms for this group was 13.1 months.

A second group consisted of six patients who had symptoms of local failure for an average duration of 12.7 months. However, they experienced symptoms of distant metastases during the terminal period of their course, which was considered to be within two months of their demise.

The pelvic symptoms that were experienced by these two groups included pelvic and/or perineal pain, perineal fistula and abscess, prostatic and bladder invasion with obstruction, hydronephrosis, uremia, bowel obstruction, edema of the lower extremities and invasion of adjacent pelvic bone. Many patients received palliative radiotherapy to the pelvis with transient to no significant relief of symptoms. Seven patients were known to have a cordotomy and/or a phenol block in an attempt to control pelvic pain.

A third category included 11 patients who experienced symptomatic distant metastases without symptomatic pelvic disease. This group represented 19.6% of those that had tumor failure, and had an average duration of symptoms of 8.3 months. Four of these patients had symptoms of hepatic failure and pain. A fifth patient died with jaundice, and at autopsy had obstruction of the biliary ducts by nodes enlarged with metastatic tumor. No intrahepatic disease was found. Other patients presented with metastasis to the lung in two, to the brain in two, retrobulbar metastases in another, and the eleventh patient had metastases to the first lumbar vertebra with resultant spinal cord compression as the only manifestation of his tumor failure.

A fourth group contained six patients who had symptoms of both local and distant failure. Most of the patients in this group failed rapidly following

TABLE 5

LOCATION OF SYMPTOMATIC FAILURES VS. STAGE						
	B <sub>1</sub>	B <sub>2</sub>	C <sub>1</sub>	C <sub>2</sub>	Total	Percent
Local symptoms only	4	9	0	19	32	57.1%
Local with terminal D.M.	2	0	1	3	6	10.7%
Distant metastases only	1	6	0	4	11	19.6%
Local and D.M. symptoms	0	4	0	2	6	10.7%
No symptoms	0	0	0	1	1	1.8%
Total	7	19	1	29	56	100%

TABLE 6

ONSET OF SYMPTOMATIC FAILURE VS. LOCATION OF FAILURE					
	Local	Distant	Both	Total	Accum %
3 months	3	0	2	5	9.1%
6 months	10	0	1	11	29.1%
Year - 1	13	1	0	14	54.5%
2	4	4	1	9	70.9%
3	1	2	1	4	78.2%
4	1	3	1	5	87.3%
5	2	1	0	3	92.7%
6	0	0	0	0	92.7%
7	2	0	0	2	96.4%
8	2	0	0	2	100 %
Total	38	11	6	55	
Asymptomatic failure - 1					

presentation as three died within two months and two others died within six months. However, the sixth patient lived for 25 months with pains from perineal and pelvic masses and with jaundice. Her prolonged course is related to a good response with chemotherapy and radiotherapy.

A fifth category includes one patient who had no symptoms of tumor failure. He died over 2 and one-half years after surgery from intercurrent disease, and at autopsy a 3 millimeter nodule of metastatic tumor was found on the surface of the liver.

If the first two local groups are combined, then 67.9% of those who had tumor failure had symptoms of local pelvic failure as the only or predominant factor affecting their quality of survival. If we also include the fourth category, then 78.6% of patients with failure had pelvic disease as a component of their symptomatology.

Table 5 also analyzes the symptomatic failures by location vs. initial extent of disease. The results unexpectedly reveal that seven of the eleven patients that had distant metastases alone had either B<sub>1</sub> or B<sub>2</sub> lesions. In addition, 23 of the 30 failures from C lesions occurred locally.

In the two patients that had a liver nodule found at the time of AP resection, and from whom all known tumor was removed, one had onset of symptoms of liver disease 27 months after surgery. These symptoms continued until her demise eight months later without evidence of local recurrence. The other patient had local tumor failure 12 months postoperatively. He had severe symptoms of local disease for the following 19 months, requiring several courses of radiotherapy and a phenol block. In addition, he had symptoms of liver pain for the last seven months of his life.

TABLE 7

5-YEAR SURVIVAL					
	Alive		Dead		5-Year Survival
	No CA	CA	No CA	CA	
A	1	0	0	0	100%
B <sub>1</sub>	20	3	11	4	60.5%
B <sub>2</sub>	14	1	4	12	48.4%
C <sub>1</sub>	3	0	1	1	60%
C <sub>2</sub>	7	2	3	21	27.3%
Total	45	6	19	38	47.2%

The patient that had a lung nodule on chest x-ray at the time of surgery, which eventually was diagnosed to be metastasis, had local failure with perineal pain beginning two months following surgery, and went on to die nine months later. He never developed symptoms from his lung lesion.

#### Onset of Symptomatic Failure

Table 6 demonstrates that 29.1% of failure occurred within six months of surgery. By the end of the first year, 54.6% had failed, 78.2% at the end of three years, and 92.7% by the fifth year.

Table 6 also evaluates the onset of symptomatic failure by its location. Thirty-four and two-tenths percent of local failures occur within six months of surgery and 68.4% within one year. However, only one of 11 from the distant metastases alone category presented during the first year.

#### Five-Year Survival

The absolute survival was calculated with 101 evaluable patients at risk for over five years. No patients were lost to follow up. In addition, seven of the nine patients who died within three months of surgery were included, as their surgery was performed over five years ago. The results are listed in Table 7. Five-year absolute survival, according to the classic Dukes' classification, is: Dukes A-24 of 39 patients or 61.5%, Dukes B-15 of 31 patients or 48.4%, and Dukes C-12 of 38 patients or 31.6%. These results are comparable to those reported from several major university centers.<sup>8,11-13</sup>

#### Effect of Inclusion of Reoperations and Marginal Resections

As stated in the Methods section, five patients were included who had recurrence from previous anterior resection, and seven who were either technically not resectable or had histological margins positive for tumor. One of the latter is not eligible for five-year follow up. If these, 11 patients were eliminated from the study group, then the failure rate for B<sub>2</sub> lesions would be 16 of 33 or 48.5%, and for C<sub>2</sub> lesions it would be 21 of 29 or 72.4%. No significant effect on location of recurrences was noted.

Five-year survival would have been improved since B<sub>2</sub> and C<sub>2</sub> lesions would have a five-year absolute survival of 51.9% and 34.6% respectively. The overall five-year survival would have been 51.6%. The classical Dukes staging provided five-year sur-

vival data as follows: A-24 of 39 patients or 61.5%, B-14 of 27 patients or 51.9%, and C-12 of 31 patients or 38.7%.

## DISCUSSION

The importance of local recurrence as a source of failure for rectal adenocarcinoma is demonstrated by the Portland, Maine experience. Local failure occurred as the only symptomatic manifestation of tumor recrudescence in 57%, and as the predominant manifestation in another 11%. Of additional importance, patients suffered from these symptoms for a considerable time, averaging over one year's duration.

The significance of local failure from colorectal adenocarcinoma has recently been stressed in two significant papers. Gunderson and Sosin<sup>9</sup> analyzed incidence and areas of failure in Wangenstein's series of second and symptomatic look re-operations. This procedure was performed on those patients with extra-rectal spread of disease and negative nodes, and on patients with positive nodes. Evidence of cancer failure was found in five of six (83%) with tumor extending through the wall with negative nodes, 29.4% (5/17) if within the wall and positive nodes (C<sub>1</sub>), and 85% (34 of 40) with C<sub>2</sub> lesions. Of great significance was that 48.1% of patients with failure had evidence of only local failure whereas only 7.7% had evidence of distant metastases alone. Of the total re-operation group, 92.3% ultimately had a component of local recurrence and 51.9% had a component of distant metastases.

Cass, Million, and Pfaff<sup>10</sup> analyzed 280 patients with adenocarcinoma of all regions of the colon. Sixty percent or 63 of 105 patients with tumor failure presented with local failure alone, 26% with distant metastases alone, and 14% with concomitant local and distant metastases. Of the 63 patients that presented with local disease, over 75% remained free from distant metastases for a two-year period.

No major progress has been made in the control of adenocarcinoma of the rectum and rectosigmoid for the past three decades. Nationally, about 50% of patients with this tumor will die from it. It is reasonable to assume that future surgical advances alone will not significantly improve the control rate of this disease over that obtained with the AP resection. Several studies have been published which indicate that adjuvant radiotherapy may improve both the control of local disease and increase the survival rate from this neoplasm.

Roswit and Higgins<sup>2</sup> have reported beneficial results from low dose preoperative radiotherapy. They strictly randomized 700 patients into operation alone vs. preoperative radiotherapy. Patients were followed for a minimum of five years. A preoperative dose equivalent to 2000 to 2800 rads was delivered to rectal lesions. Of 414 patients that had AP resections, five-year survival was 40.8% for treated patients and 28.4% for control. This represents a 44% increase in survival. At operation, 28% of

preoperatively radiated patients had positive nodes, while 40% of controls had nodes involved. In analysis of 115 autopsies, local failure was decreased 40% to 29% and distant metastases was decreased 63% to 47% in treated groups.

Kligerman, et al<sup>3</sup> obtained similar beneficial results with 4500 rad preoperative radiotherapy in a small randomized group at New Haven.

Stevens, Allen, and Fletcher<sup>1</sup> delivered high dose (5000-6000 rads) preoperative radiotherapy to 57 bulky resectable lesions, and 40 unresectable or inoperable rectosigmoid carcinomas. In the resectable patients, the five-year survival was 53% and they had only one pelvic recurrence. In the unresectable group, 16 of 40 patients then had abdomino-perineal resections. Three remained alive without disease and two died without evidence of cancer.

The value of postoperative radiotherapy had been dealt with in several recent papers. Gunderson, et al<sup>5</sup> treated 40 patients with colorectal tumor that extended through the bowel wall and/or had positive nodes. Only one of 31 curative resections have recurred locally. Twenty-three and five-tenths percent developed distant metastases.

Withers and Romsdahl<sup>6</sup> from M.D. Anderson Hospital treated 26 patients with rectal carcinoma extending through the bowel wall with postoperative radiotherapy. Patients were followed for 12 to 40 months and only one has developed local recurrence and 20 are still free of disease.

Turner, et al<sup>7</sup> gave postoperative radiation therapy to 19 colorectal tumors. Two patients developed local recurrence. The total number of patients treated from these three papers is 89, with a local recurrence rate of 4.5%.

There is disagreement among radiation oncologists concerning whether preoperative or postoperative radiation therapy should be recommended.

The arguments for preoperative radiotherapy are:

1. Dissemination of cancer at the time of surgery can be diminished by preoperative radiotherapy.
2. Preoperative radiotherapy can convert unresectable or borderline resectable lesions to ones that can be curatively resected.
3. In those patients that have difficulty with perineal healing following AP resection, the start of postoperative radiotherapy may be delayed for two to four months. By this time, local recurrences may have become too large to control with tolerable doses of radiation. In our series, 11% of the local recurrences presented within three months of surgery, and 36% presented within six months.

The major arguments for postoperative radiotherapy are:

1. The extent of pathology can best be established at the time of surgery if no preoperative radiotherapy is given. If the patient has advanced liver, or upper abdominal disease, or

lack of extra rectal and/or nodal involvement, then adjuvant radiotherapy may not be needed. In addition, if tumor involves bladder or uterus, then lack of preoperative radiotherapy will better allow the surgeon to evaluate the extent of resection needed.

2. Preoperative radiotherapy is considered by some surgeons as a relative contraindication to an anterior resection. However, a recent study<sup>14</sup> using temporary diverting colostomies or using the proximal anastomotic loop from unirradiated colon reported good results with anterior resection following 5000 rad radiotherapy.

Besides adjuvant radiotherapy, chemotherapy has been used in an attempt to improve surgical results. Two recent studies<sup>15,16</sup> have suggested a beneficial effect of adjuvant chemotherapy. Further studies are in progress and hopefully will define the efficacy of this modality.

### CONCLUSION

The high risk of failure following AP resection alone for rectal and rectosigmoid adenocarcinomas that extend through the full thickness of the bowel wall, or that have metastases to regional lymph nodes, is evident from this and other reported series. In addition, the morbidity of local recurrence dominates the quality of survival in those patients who expire from this disease. On the basis of recent reports, radiotherapy should be helpful in significantly increasing the survival rate. However, if adjuvant radiotherapy does nothing more than decrease the local recurrence rate, then the quality of life in those patients who eventually fail from this tumor will be markedly improved. Thus, radiotherapy should be used in conjunction with surgical resection in those patients with B<sub>2</sub> or C lesions.

### COMMENT

Dr. Gilbert is to be congratulated on a very complete and thorough evaluation of a large group of people undergoing abdominal perineal resection in the Portland hospitals over a ten-year period. The problem of local recurrence has always haunted surgeons in an attempt to better control this unfortunate disease. The careful analysis by Dr. Gilbert of those patients who had local recurrence clearly indicates that when the tumor has extended through the full thickness of the wall or who have positive lymph nodes are an extremely high risk for local recurrent disease. With modern techniques of radiotherapy, it would indeed appear that an excellent case can be made for either preoperative or postoperative radiation therapy in that select group of patients. Several articles have also appeared in the recent literature indicating similar experience from other institutions although opinion is divided as to the value of postoperative radiation in some series.

It would appear, however, that with the evidence that Dr. Gilbert has presented to us that all surgeons who perform abdominal perineal resection for adenocarcinoma of the rectum should therefore give strong consideration for adjuvant radiation therapy in an attempt to prevent local recurrent disease.

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# A Method for Improving the Use of Constant Infusion Drugs in Cardiothoracic Patients

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## INTRODUCTION

Improvement in the post-operative management of cardiac surgical patients ranks in importance with proper patient selection and good operative technique in assuring optimum results. There is no substitute for close, bedside monitoring of cerebral function, urinary output, and peripheral perfusion in assessing adequate cardiac output. Determination of arteriovenous oxygen content difference and actual measuring of cardiac output by thermodilution methods may confirm one's impression of the clinical situation. Once a low cardiac output state is diagnosed and the need demonstrated for drugs that improve cardiac function, proper administration of these drugs is necessary to reverse a potentially fatal trend.

The purpose of this report is to present a method used at Maine Medical Center to assure effective use of drugs that affect cardiovascular function and minimize potential adverse side effects.

## DISCUSSION

Dopamine is an example of a drug that may be needed to improve cardiac inotropic function. Its effective dose range in micrograms per kilogram per minute and unwanted side effects are well known.<sup>1,2</sup>

In the past at Maine Medical Center, dopamine solutions were made by adding one or two ampules (200 mg or 400 mg) to 500 milliliters of intravenous fluid. This solution was administered to the patient at a rate necessary to maintain an adequate blood pressure while other variables such as central nervous system function, urinary output, and peripheral pulses were carefully checked. The actual dose of dopamine in micrograms per kilogram per minute (mcg/kg/min) was not always known. Instead, the dopamine rate was reported simply as so many drops of intravenous fluid per minute. Because of frequent changes in the rate of administration of the dopamine solution and variation in weight from patient to patient, it was inconvenient to calculate the drug dose (in mcg/kg/min).

Without knowledge of the actual drug dose (in mcg/kg/min) necessary to maintain adequate car-

diac function, the physician treating a patient with cardiogenic shock might not appreciate the seriousness of the situation. A patient needing 10-15 mcg/kg/min of dopamine to improve cardiac performance likely has more serious cardiac impairment at that moment than the patient who responds to 2-5 mcg/kg/min of the drug. On the other hand, high doses of the same drug may not produce the desired improvement in cardiac function without adverse effects such as arrhythmia or increased peripheral vascular resistance. Knowledge of the drug dose in mcg/kg/min under these circumstances helps to decide whether substitution or addition of another, more effective drug is necessary.

For example, suppose that a patient weighing 80 kilograms has had a myocardial infarction and develops a low cardiac output state as evidenced by falling blood pressure, impairment of cerebation, decreasing urinary output, and poor peripheral perfusion. The pulmonary capillary wedge pressure is 18 mm Hg, indicating that there has been adequate volume replacement. The patient needs improvement in the inotropic function of the heart and receives a solution of dopamine (200 mg in 500 ml) which is increased in rate until 75 ml/hr is reached. At this point, the 80 kilogram patient is receiving 6.3 mcg/kg/min of dopamine. If the dose of dopamine that will give the needed improvement in cardiac function is 10 mcg/kg/min, then the rate of the drug solution will have to be increased further from 75 ml/hr to 120 ml/hr. Without knowing the actual dose (in mcg/kg/min), the physician might hesitate to increase the rate of drug administration thinking that the patient's condition is so serious that there will be no further response. The amount of fluid being given either at 75 ml/hr or 120 ml/hr is excessive considering the restriction that should be placed on a patient with already high left sided cardiac filling pressure. Even though higher concentrations of drug are used (400 mg or 800 mg in 500 ml) in order to decrease the amount of fluid administered, the dose of drug (in mcg/kg/min) will not be known unless it is calculated for the particular concentration of drug, patient weight, and intravenous fluid rate.

It is clear from the above example that the complications of ineffective drug therapy and fluid overload may grow out of lack of knowledge of actual drug dose. Because of this, we have devised standard concentrations of dopamine based upon the patient's weight (Table 1). This is done by multiplying the patient's weight by the correct factor to

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TABLE 1

DOPAMINE CONCENTRATIONS	
ADMINISTRATION BY IVAC*	
Concentration	mcg/kg/ml
A	10
B	20
C	50
ADMINISTRATION BY HARVARD PUMP**	
Concentration	mcg/kg/ml
D	50
E	100
F	200

\*IVAC Corporation, San Diego, Ca.

\*\*Harvard Apparatus, Millis, Mass.

TABLE 2

WEIGHT MULTIPLICATION FACTORS FOR VARIOUS DRUG CONCENTRATIONS			
CONCENTRATION (mcg/kg/ml)	TOTAL VOLUME solution (ml)	FACTOR (kilograms)	FACTOR (pounds)
10	500	5	2.27
20	500	10	4.54
50	500	25	11.35
50	50	2.5	1.14
100	50	5	2.27
200	50	10	4.54

determine the amount of dopamine to be added to intravenous fluid. For example, if 400 milligrams of dopamine is added to 500 milliliters of solution, the resultant concentration of drug is 0.8 mg/ml or 800 mcg/ml.

$$400 \text{ mg} \div 500 \text{ ml} = 0.8 \text{ mg/ml} \quad (1)$$

$$0.8 \text{ mg/ml} \times 1000 \text{ mcg/mg} = 800 \text{ mcg/ml} \quad (2)$$

For the patient weighing 80 kilograms, this solution contains 10 mcg/kg/ml.

$$800 \text{ mcg/ml} \div 80 \text{ kg} = 10 \text{ mcg/kg/ml} \quad (3)$$

Originally, 400 milligrams or 5 times the patient weight (80 kg) was added to 500 milliliters.

$$5 \times 80 = 400 \quad (4)$$

To make a solution containing 10 mcg/kg/ml of a drug to a 500 ml volume, simply multiply the patient's weight in kilograms by five to find the milligrams of drug to be added. If the concentration of drug is to be 20 mcg/kg/ml made to a 500 ml volume, then 10 times the weight in kilograms is the correct amount (10 × 80 for the 80 kg patient or 800 mg in 500 ml). To make a concentration of 10 mcg/kg/ml to a 250 ml volume, the factor is 2.5 times the weight in kilograms. If the weight in pounds is used, then each of the factors above should be divided by 2.2. For example, if the patient weighed 176 pounds (80 kg), then the weight in pounds would be multiplied by 2.27 (5 ÷ 2.2) to calculate the milligrams of drug to be added to 500 milliliters to make a 10 mcg/kg/ml solution (2.27 × 176 = 400).

Table 2 is a complete listing of dopamine concentrations used at Maine Medical Center with the appropriate multiplication factors for the weight either in kilograms or pounds. Concentration A (10 mcg/kg/ml) is the most commonly used dopamine solution at our hospital. Based on our experience in

PT: BROWN JOHN  
DOPAMINE CONCENTRATION A (10MCG/KG/ML)

	ML/HR	MCG/KG/MIN		
	75	12.5	D	
	70	11.7	O	
I	65	10.8	P	DOSE RANGE
V	60	10.0	A	
A	55	9.2	M	2 to 40
C	50	8.3	I	MCG/KG/MIN
	45	7.5	N	
R	40	6.7	E	
A	35	5.8		
T	30	5.0	D	
E	25	4.2	O	
	20	3.3	S	
	15	2.5	E	
	10	1.7		
*RETURN	5	0.8		PRINT & REVIEW

Fig. 1. This is the IV rate — drug dose table for dopamine concentration A (10mcg/kg/ml) for IVAC use taken from a video matrix display at Maine Medical Center.

PT: BROWN JOHN  
DOPAMINE CONCENTRATION B (20MCG/KG/ML)

	ML/HR	MCG/KG/MIN		
	75	24.0	D	
	70	23.4	O	
I	65	21.6	P	
V	60	20.0	A	
A	55	18.4	M	DOSE RANGE
C	50	16.6	I	
	45	15.0	N	2 to 40
R	40	13.4	E	MCG/KG/MIN
A	35	11.6		
T	30	10.0	D	
E	25	8.4	O	
	20	6.6	S	
	15	5.0	E	
	10	3.4		
*RETURN	5	1.6		PRINT & REVIEW

Fig. 2. This is the IV rate-drug dose table for dopamine concentration B (20 mcg/kg/ml) for IVAC use taken from a video matrix display at Maine Medical Center.

using dopamine, the concentration of 10 mcg/kg/ml was chosen to avoid excessive fluid administration rates when the average effective dose of drug is used (25 to 50 ml/hr for 4 to 8 mcg/kg/min). The more concentrated solutions give complete coverage of the recommended dose range.

By making standard solutions in mcg/kg/ml, the dose of drug in mcg/kg/min will be the same from patient to patient if the rate of infusion is the same, whether the patient is 40 kilograms or 80 kilograms. This allows us to make an IV fluid rate — drug dose table when a particular concentration of drug in mcg/kg/ml is ordered (Figure 1). This figure gives valuable information regarding the dose range, the intravenous fluid rate in ml/hr for proper recording of intake and, most importantly, the dose of the drug in mcg/kg/min for the particular fluid rate. If it is found that the patient is receiving a large amount of fluid to deliver an effective dose of drug then the next higher concentration of drug solution may be ordered to decrease the fluid rate but continue the same effective dose of drug (Figure 2).

PT: BROWN JOHN  
DOPAMINE CONCENTRATION D (50MCG/KG/ML)

	SETTING	ML/HR	MCG/KG/MIN	
H	1-----	0.9-----	0.8	D
A	2-----	1.3-----	1.1	O
R	3-----	1.9-----	1.6	P
V	4-----	2.6-----	2.2	A
A	5-----	3.6-----	3.0	M
R	6-----	5.1-----	4.2	I
D	7-----	6.1-----	6.0	N
	8-----	10.0-----	8.0	E
P	9-----	14.0-----	11.0	
U	10-----	20.0-----	15.0	D
M				O
P				S

(DOSE RANGE: 2-40MCG/KG/MIN)

\*RETURN

PRINT & REVIEW

Fig. 3. This is the IV rate-drug dose table for dopamine concentration D (50 mcg/kg/ml) for Harvard pump use taken from a video matrix display at Maine Medical Center.

DOPAMINE DOSAGE COMPUTATION

NOTE: 1) FILL IN THE APPROPRIATE BLANK,  
THEN HIT 'SEND' KEY

DOPAMINE CONCENTRATION A (10MCG/KG/ML)

-----\*2.3 or -----\*5  
(LBS) (KG)

DOPAMINE CONCENTRATION B (20MCG/KG/ML)

-----\*4.6 OR -----\*10  
(LBS) (KG)

\*RETURN

\*ERR \*NEXT FOR CONC C (50MCG/KG/ML)

Fig. 4. This is the dopamine dosage computation display for concentrations A and B taken from a video matrix display at Maine Medical Center.

All drug solutions administered in this way are controlled either by IVAC or Harvard pump and, in the case of dopamine, preferably through a central venous line. For adults, concentrations A, B, and C above are made to 500 ml volumes and given by IVAC. For pediatric patients, the concentrations D, E, and F made to 50 ml volumes are given by Harvard pump. Because of the higher concentration of drug in mcg/kg/ml, a slower rate (less fluid per hour) can be used to deliver an effective dose of drug without the risk of fluid overload in the child (Figure 3).

In the event of an emergency where dopamine must be given without delay, 400 milligrams is added to 500 milliliters of intravenous fluid and the rate selected that gives adequate patient response. When the patient's condition stabilizes on this emergency concentration of drug and his weight is known, the current drug dose in mcg/kg/ml is calculated. Then one of the standard concentrations of dopamine in mcg/kg/ml is chosen depending on the patient's fluid restriction and drug dose requirements. Table 3 shows the equations for converting from ml/hr to mcg/kg/min.

Since Maine Medical Center uses the Medical Information System (MIS),\* all orders are handled

\*Technicon Medical Information Systems Corp., Mountain View, Ca. 94040.

TABLE 3

ML/HR TO MCG/KG/MIN CONVERSION

Fill in blanks as follows:

1) Infusion rate in ml/hr

2) Weight in kilograms

Solution Concentration	Equation	
200 mg/500 ml -----	$6.67 \times \frac{\text{ml/hr}}{(1)} \div \frac{\text{kg}}{(2)} = \text{mcg/kg/min}$	
400 mg/500 ml -----	$13.33 \times \frac{\text{ml/hr}}{(1)} \div \frac{\text{kg}}{(2)} = \text{mcg/kg/min}$	
800 mg/500 ml -----	$26.67 \times \frac{\text{ml/hr}}{(1)} \div \frac{\text{kg}}{(2)} = \text{mcg/kg/min}$	

by computer. The above method of dose calculation and drug administration lends itself very well to this system. After selecting dopamine from the pharmacy list of drugs, the desired concentration of drug is chosen. The weight in kilograms is entered by typing in the appropriate blank on the video matrix display depending upon the concentration of drug desired. Then several calculations are done (Figure 4). The first answer is the milligrams of dopamine to be added to the solution. In the case of dopamine concentration A (10 mcg/kg/ml), the drug is added to 500 milliliters of intravenous fluid. Another calculation is done that tells what volume of dopamine stock solution (40 mg/ml) corresponds to the milligrams of dopamine. This second calculation decreases the chance of drug error in making the solution. As the drug is ordered, an IVAC rate-drug dose printout is automatically made with the patient's name, the concentration of drug (mcg/kg/ml), the IVAC rate in ml/hr corresponding to the drug dose in mcg/kg/min (Figure 1). The dose range for the particular drug is also included. This print-out is taped to the IVAC machine or Harvard pump for easy reference. Similar dose computations and print-outs are available for nitroprusside, nitroglycerin, and epinephrine and are being developed for Isuprel® and lidocaine.

The method presented above for the administration of drug solutions is applicable to any drug where constant infusion is necessary and it is important to know the actual drug dose in micrograms per kilogram per minute. Although we use a computerized system for drug dose computation and ordering, the method can be used in any hospital where accurate knowledge of drug doses is wanted. The weight multiplication factors and the respective IV rate-drug dose tables can be kept available in intensive care units where these drugs are to be used.

SUMMARY

The dose in micrograms per kilogram per minute (mcg/kg/min) for constant infusion drugs that affect cardiovascular function should be known at all times to prevent the complications of inadequate drug dose and therapeutic failure or drug overdose and unwanted side effects. In addition, different concentrations of drug solutions should be available

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# PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

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*The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.*

*The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.*

## **The Advantages**

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy—and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

## **The Disadvantages**

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information

is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

## **The Solution**

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

**PMA**

THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION  
1155 FIFTEENTH ST. N. W. WASHINGTON, D. C. 20005

# Review of the Clinical Usefulness of the Serum Ferritin Determination

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Until recently, ferritin, an iron (Fe) storage protein found mainly in the liver and spleen, was not felt to be present in the circulation, except under pathologic conditions. With the development of a radioimmunoassay technique, ferritin has been found in the blood of normal subjects.<sup>1</sup> Work subsequently has been done to correlate the levels of serum ferritin with iron stores in health and disease. A relatively inexpensive enzyme immunoassay is now commercially available.<sup>2</sup> The purpose of this paper is to analyze the published data to determine what role the serum ferritin assay may have in the evaluation of iron storage disorders.

The ferritin molecule consists of an outer apoferritin protein shell surrounding a core of one or more micelles of storage iron. Each molecule can contain up to 4,500 Fe atoms, but normally holds less than 3,000, allowing for a reserve capacity. Its configuration allows for rapid uptake and release of Fe. The ferritins isolated from different organs have differing mobilities on gel electrophoresis related to small differences in the amino acid sequence of the 24 monomers which form the apoferritin shell. Of the isoforms, the one of particular clinical importance is serum ferritin, which appears related to the level of storage iron.<sup>3</sup> The precise role of ferritin in Fe homeostasis is largely unknown. Ferritin protein and ferritin iron are increased soon after intraperitoneal injections of iron in rats. Cellular ferritin production *in vitro* is directly stimulated by increasing the Fe level in the medium.<sup>4</sup> Ferritin may be secretory protein, synthesized on endoplasmic reticulum bound RNA. The Fe content of ferritin is easily exchangeable. However, when it undergoes a partial degradation it is transformed into the much less bioavailable hemosiderin.

Fe is absorbed from the small intestine, a process known to be determined by the body's total iron stores. Once absorbed, the extracellular pool, primarily composed of transferrin bound iron, is in dynamic equilibrium with the intracellular pool. This extracellular pool consists of ferritin, hemosiderin, and other iron containing proteins.<sup>5</sup> Changes in iron storage should be reflected in all these components, including the level of serum ferritin.

The parameters used to assess a patient's iron

storage status are hemoglobin, red cell indices, serum iron, total iron binding capacity (TIBC), percent transferrin saturation, and visible iron on bone marrow examination. Iron chelator excretion assays and quantitative phlebotomy are used in the research setting. In 1972, Addison, et al,<sup>4</sup> described a radioimmunoassay which detected ferritin in the sera of normal adults. Males were found to have an average serum ferritin level of 52 ng/ml (12-128), and females 29 ng/ml (10-56). In the study, patients with known iron deficiency had a mean hemoglobin of 9.1 gm% serum iron of 22 mg% with a percent transferrin saturation of 5% and a mean ferritin level of 5 ng/ml (.6-12). Patients with iron overload had ferritin levels of greater than 1,000 ng/ml.

Walters, et al<sup>6</sup> compared the level of serum ferritin in normal subjects with the iron stores as determined by quantitative phlebotomy. This technique, in normals, depletes the body of its available stores. A linear relationship was found between these two parameters. Serum ferritin levels were seen to drop early in phlebotomy, before the percent saturation of transferrin, in parallel to the previously reported pattern of visible bone marrow iron stores. However, this study did not correlate bone marrow specimens with the ferritin data. Subsequent studies have confirmed the initial findings in normal subjects, patients with iron deficiency, and patients with iron overload, such as primary and secondary hemosiderosis, thalassemia, and refractory anemia treated with multiple transfusions.<sup>5,6,7,8,9</sup> In fully developed hemochromatosis, the serum ferritin level is grossly elevated but is usually normal in early states despite high iron levels in the serum and high chelatable storage iron.<sup>5</sup>

Siimes, et al<sup>8</sup> have shown that serum ferritin levels parallel the known stores of iron in childhood. At birth the mean concentration of serum ferritin is 101 ng/ml. During the first postnatal month, there is a steep rise to a mean of 356 ng/ml. The fall to 30 ng/ml at six months of age persists to adulthood. Children with iron deficiency and with iron overload were also studied. Levels of serum ferritin correlated well with the known iron storage status in these disease states.

One of the proposed uses for serum ferritin is in the evaluation of the anemia of chronic disease. This diagnosis is often used to designate any anemia seen in conjunction with a chronic disease state. More appropriately, it is a hypochromic or normochromic anemia, associated with a low serum iron and total iron-binding capacity, variable percent transferrin

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saturations, and increased stainable iron in the bone marrow. The definitive diagnostic procedure is the bone marrow examination which reveals increased stores despite a hypochromic or normocytic anemia with a low serum iron. Recently the serum ferritin level has been suggested as a simpler procedure with equivalent yield. Elevated ferritin levels should be expected in this situation where iron stores are increased. Bentley and Williams<sup>10</sup> studied 60 patients with rheumatoid arthritis and anemia. They subdivided patients by the visible iron stores in the bone marrow (from 0 to 3+). Patients without visible iron stores had a mean serum ferritin of 38 ng/ml ( $\pm$  19). In contrast, iron deficient patients without arthritis have been shown to have serum ferritin levels of less than 12 ng/ml. In patients with arthritis and anemia with iron present in the marrow, there was only a rough correlation of mean serum ferritin levels with the stainable bone marrow iron. The levels were generally higher than would be expected in normals with equivalent stores; and wide ranges of values were noted in each subgroup. For example, in patients with 2+ iron stores serum ferritin levels ranged from a low of less than 30 ng/ml to a high of greater than 650 ng/ml.

High levels of serum ferritin have also been found in other pathologic states including hepatomas, metastatic tumors in liver, breast and pancreatic carcinoma, and most hematologic malignancies.<sup>8,11,12,13</sup> Acute inflammatory conditions including upper and lower respiratory infections and gastroenteritis, and renal and liver disease have also been associated with elevated serum ferritin levels.<sup>8</sup> The elevated ferritin levels in these acute and chronic clinical states may be influenced by a number of factors, including total-body iron stores, release of ferritin from inflamed tissue, production of ferritin by proliferating tumor cells, and production of isoferritins.

In summary, the serum ferritin level correlates with other indicators of iron storage status in health and in the iron deficient patient. In states of iron overload serum ferritin levels are high. However, in early primary hemochromatosis the serum ferritin level is normal despite high iron levels in the serum, high intestinal iron absorption rates, and high chelatable iron stores. In patients with "the anemia of chronic disease", the levels of ferritin are elevated; but the pathogenesis may be multifactorial with increased marrow iron stores only one element. The serum ferritin assay may have usefulness in the evaluation of iron deficiency and overload; but a

reliable diagnosis of these conditions can usually be made by other available means. In the evaluation of the anemia of chronic disease, the bone marrow examination for stainable iron remains the definitive test, with the serum iron and iron-binding capacity aiding significantly. Further studies directed at correlating the levels of serum ferritin with stainable iron stores in the bone marrow and elucidating the pathophysiology of elevated ferritin levels in different pathologic conditions may establish the role of serum ferritin in the evaluation of iron storage disorders.

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# Psychological Management of the Patient With Recurrent Affective Disorder

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In the last decade, psychiatric research has made significant contributions to our understanding of normal and abnormal neurophysiology.<sup>1</sup> The greatest advances have been made in the area of affective disorders. Happily, the increase in understanding has been paralleled by new treatment options. The development of tricyclic antidepressants and the release for general use of lithium carbonate have immensely reduced the human misery of mood disorders. It is no wonder that the literature emphasizes biologic approaches to depression and mania. The emphasis is timely and justified. However, experienced clinicians realize that medications are only effective when administered in the context of a satisfactory doctor-patient relationship. This, therefore, is the first of two papers on treatment of these patients. The next paper will discuss the practicalities of drug administration, while this will enhance the physician's understanding of common issues in the doctor-patient relationship in patients with affective disorder treated in an outpatient setting.

For the purpose of simplicity, this article will assume only two clinical types — the patient with highs and lows (bipolar) and the patient with only lows (unipolar). Although this taxonomy is inadequate for refined diagnosis, it is most satisfactory for psychological generalizations.

## TACTICAL CONSIDERATIONS

The doctor-patient relationship issues pertinent to affective disorder patients include but transcend the basic rules of decency, respect, and clarity. The following is a discussion of problems and tactics that should be considered early in the treatment.

(a) *Trust*. In both depressive and manic illness, paranoid trends may be evident, and trust is difficult. In periods of normal mood, patients may seem to trust, but remain inwardly doubting of the physician's concern. Bipolar patients are deceptively gregarious; they give an illusion of trust which dissolves rapidly with a mood change. Unipolar patients feel worthless and unlovable; they are often suspicious of the physician's apparent concern.<sup>2</sup> The physician must always be sensitive to evidence of mistrust. The depressive may conceal information in hidden sullen anger; the manic may seem to be in full compliance with treatment but in adolescent fashion cheek his medication or flush it down the toilet. No matter how socially facile the patient appears, the physician should remember these patients doubt their relationship with others.

(b) *Nurturance*. The physician who treats depressives easily recognizes their excessive needs for love, affection, attention, and magic to counteract the relentless self-criticism of their consciences.<sup>3</sup> They take in the physician's attention as an infant takes milk and with approximately the same results; in a few hours all that good attention has gone out of their system, and they need to be fed again.

It is easy to assume that the dependence and need for nurturance disappear with the depression. However, the treated depressive continues to require great emotional support; he has a fragile self-esteem which plummets quickly with the withdrawal of such support. These patients should not be told to "call me if you get depressed again." Such an approach fails to recognize the need for ongoing nurturance. It is true, however, that the physician must wean the patient, since no one has time to offer in an ongoing way that time and attention which was offered during a depression, but the physician must resist the temptation to terminate. Periodic visits, no matter how infrequent, are very helpful.

The hypomanic patient also has great needs for nurturance, but he maintains the illusion that he can feed himself. His gregariousness and his gambler's psychology often make it appear that he can nurture himself and the rest of the world, too. This illusion, however, is thinly veiled in alcohol excess, gambling, recklessness, etc. Untreated, he may progress to a rambling, chaotic manic state in which even personal hygiene is too great an effort.

Bipolar patients are deceptive: the physician is easily captivated by their manic style and when they are stabilized fails to appreciate their great neediness and their marked inability to establish intimate and mature interpersonal relations. Their manic schemes are exciting and may seem more adaptive than the dull life of the physician. Often the bipolar patient will test the physician's appreciation of the manic illusion. The patient may propose that he move to another state, change jobs, etc., in essence, a series of magical maneuvers to deny his extreme dependency. He may even suggest that the physician get involved in such schemes. The physician must be prepared for such testing behavior.

(c) *Insight*. Although the treatment of most affective disorder patients does not generally involve formal psychotherapy, the physician must interest the patient in his illness to facilitate treatment. The physician encourages the patient to gain an objective view of his disorder so the two of them can watch the process together and in alliance can

minimize its harmful effects. The ascendancy of biological psychiatry has given Manic Depressive Illness considerable status. To some patients all things are now possible through chemical treatment, and correspondingly, all undesirable behavior is the direct result of bad brain neurochemistry. There is, therefore, a paradox in this: to gain a patient's alliance, the physician must stress the biological (non-motivational) aspects of the patient's behavior at the expense of minimizing the motivated conscious elements. For some patients their marital misconduct, irresponsibility at work, etc., can all be rationalized by swings in brain chemistry out of their control. This is true of the unipolar as well as bipolar patients. Recurrent depressives may take shelter beneath the excuse of "illness" to indulge themselves in unprovoked hostile attacks on their families.

The physician, therefore, must be aware of the paradox of his alliance with the patient. He is asking the patient to observe his affective disorder while at the same time separate non-biologically induced behavior from it and take responsibility for that behavior. The effectiveness of treatment depends on the success of doctor and patient in achieving this balanced view.

(d) *Compliance*. Bipolars throw the doctor's medicine away because they cannot tolerate his control of them with it. Unipolars grow discouraged with the doctor and his medicine and repeatedly forget it. Bipolars are often impulsive, self-indulgent people. They live for the moment, and such concepts as long-term chemotherapeutic maintenance are foreign to their thinking. The depressive lives rooted in the past, and the concept of taking medicine for future happiness does not fit his morbid concept of life.

Compliance must be addressed in the first interview and tactfully assessed in each subsequent interview over a period of years. The physician can never assume compliance.

In general, compliance increases with age. The more the patient experiences his illness, the more pain it causes him, the greater his compliance to treatment. The physician must have considerable patience; he should view compliance as a quality to groom over a period of years. If he is easily angered at initial noncompliances, he may not be able to sustain the doctor-patient relationship.

(e) *Lability*. As their mood shifts, both bipolar and unipolar patients shift their attitudes toward important figures. The physician with a pleasant relationship with a compensated bipolar patient may be unprepared for the antagonistic hostility which ushers in the hypomanic period. Likewise he may be unprepared for bitterness and despairing indictments of ineffectiveness by the patient who is slipping into a depression.

It is critical that the physician react to these changes with clinical sensitivity and not anger or hurt. Eventually both doctor and patient must exam-

ine these difficult labile shifts in the context of the illness.

(f) *Family Reinforcers*. Patients with affective disorder choose mates who reinforce their psychopathology. Members of a family may need the identified patient to be depressed to maintain homeostasis within the family system. Some spouses enjoy the hypomanic aspects of the manic depressive and encourage this behavior. The physician, therefore, must be aware of the forces in the family which are in alliance with his treatment plan and those which run counter to it.

### CLINICAL STANCE

The above are some of the tactical issues in the psychological management of affective disorder patients. With these in mind let us elaborate the clinical approach to the patient in both hypomanic and depressed states.

(A) *The Hypomanic*. As the patient moves from baseline mood to hypomania, several clinical styles may emerge. The hypomania may be ushered in by increased congeniality, imaginativeness, and social or business activity. At first glance this may seem to be a heightening of mental health, and impressive stride toward self-actualization. On examination, however, this state is a reflection of increasing self-centeredness, despite its extroverted appearance. It is critical that the physician confront the patient with his opinion that the state is pathological and appeal to the patient's capacity to monitor objectively his affective disorder. The physician will want to start lithium carbonate or increase it if the patient is on maintenance. Alliance with the family is critical, since their lack of support can undermine the physician's attempts.

The hypomanic patient requires a special style of intervention. The self-centeredness causes an inability to treat relationships with much depth or concern. The physician, therefore, must accentuate the intensity of his behavior to make an impact. High activity, high concern to the point of dramatic overstatement is a better stance for the physician than a more subdued professional approach. The hypomanic is actively trying to deny his dependency to prove that he needs no one. Only if the physician is endowed with "big magic" by the patient can the patient give credibility to the physician's concerns and treatment.

The patient moving into a hypomanic phase may be irritable and paranoid. The congeniality and expansive wit may only be a thin veneer.<sup>4</sup> Distrust, anger, and the beginning of delusional systems may strain the doctor-patient relationship. The physician must be prepared for this. If his self-esteem depends on the adoration by his patients, the sudden distrust or vitriolic attack may cause him to respond with guilty atonement or angry retribution. The patient may challenge the physician's credentials or his judgment. Hypomanic patients are extraordinarily intuitive in finding another's weakness. If you have

a character flaw or particular vulnerability, be prepared for the assault. The hypomanic may use anger and criticism, or he may engage the physician in a seductive battle of wits to line him up for the kill. Hypomanic patients will use professional jargon to outclass the physician. In all of this uproar, the physician must keep a steady eye on the psychopathology and not engage in a personal battle.

The physician must make a critical assessment during this period of increasing manic behavior. (1) Does he have sufficient relationship with the patient to accomplish treatment on an outpatient basis? (2) Is the patient responsible for his actions? Is he a danger to himself or others? Important variables include (a) the duration and previous effectiveness of the doctor-patient relationship, (b) the family support, and (c) the degree of mania. If the patient sees his illness as ego-alien; if he has had previous success with outpatient medications management; if the patient has faith in the physician and supports the treatment, outpatient management will be effective.

(B) *The Depressive.* Whereas, the hypomanic can be entertaining and engaging, the depressive is tedious, empty, fatiguing, or boring. The physician may have to fight the urge to let the depressive "drift away" from treatment. The psychomotor retardation and rumination makes his thinking and conversation slow and impoverished. Depressives are difficult patients with whom to be with for sustained periods, particularly if they are bipolars the physician has known in their livelier manic phase.

First, of course, the physician must determine the level of incapacitation, the suicidal risk, and the need for hospitalization. If the patient is locked in a deeply retarded psychotic depression, he must put the patient in the hospital and care for the patient as one would a small infant, i.e., with a mother's concern for nutrition, hygiene, and protection from dangerous objects or situations. The agitated depressive has similar needs but requires the vigilance of a parent toward a toddler so that the motor agitation does not wreck his health or facilitate self-destructive behavior.

Most affective disorder patients will not slip to such deeply regressed levels and can be treated as outpatients. More commonly they will be verbal, expressing concern about their depressions and asking for assistance with their fatigue, insomnia, and pervasive gloom. They need a great deal of attention but often feel guilty about receiving it. They distrust sympathy and consolation and flatly reject optimism as naive and a sign that the physician does not recognize the gravity of their situation.

The best approach for the physician, therefore, is the following:

(1) He should make a clear statement of his understanding of the depression, followed by a credible prognostic assessment, and he must repeat this frequently with confidence.

(2) He should arrange brief, frequent encounters

of an active medical diagnostic nature with questions about sleep, appetite, mood, response to drugs, side effects, suicidal ideas, etc. On an outpatient basis the contacts should be at least weekly during the severity of the depression. The clarity of the physician's diagnosis coupled with an active medical approach is of great importance to help the patient participate in his treatment.<sup>5</sup> Structured medical questioning is an acceptable form of nurturance for the depressive; receiving it does not foster guilt.

The clinical warnings about the dangerous "upswing" phase of depression are warranted.<sup>6</sup> The physician should counsel the patient as he improves and has more energy; he may experience anxiety and suicidal preoccupations. The patient should be reassured that these are not unusual and are certainly feelings in which the physician is very much interested. During this period if the patient is hospitalized, the physician must avoid the mistake of premature discharge. Many patients have suicided in the first days out of the hospital.

#### LONG-TERM COMMITMENT — THE CRUCIAL VARIABLE

Physicians often derive much of their satisfaction from the treatment of pronounced and visible acute illnesses. Both depression and hypomania fall into this category, and the temptation to lose interest in the "well" patient is great. However, it is most important to realize that these patients are never "well" in the full sense of the word; they are merely between episodes. Even in their euthymic state they are not well. Problems of dependency, childlike expectations, marital discord, alcoholism, or addiction to work trouble them. They need a stable physician figure to see them through the years. The physician should structure his follow up as he would a brittle diabetic or a marginally compensated case of COPD.

We recommend that these patients be seen regularly, regardless of their mood. During periods of normal mood, the visit may be only every month or two, but it should be a regularly scheduled visit, and the pattern should never be broken. The time of the contact may only be five minutes, but it provides a treatment time which is most helpful for these patients.

It is clear to the authors that critical life events trigger mood swings, despite the biological matrix in which they occur. The physician must understand the immense significance to these patients of death, illness, divorce, unemployment, promotion, graduation and many other emotionally charged critical events. He must actively question the patient about forthcoming situations.<sup>7</sup> He must challenge the patient's denial concerning feelings toward these events. To the extent to which the physician can anticipate stressful periods, he should schedule the patient's visits accordingly. The 40-year-old woman who is busily preparing for her daughter's wedding

should be seen a few days before the ceremony. The 35-year-old man who is changing jobs should be seen before and immediately after the change. If the physician reads in the paper that his patient with recurrent depressions has just lost a spouse, he should call the patient, express condolences, and restate his concerns and his availability.

The physician must educate affective disorder patients to call within five days of a mood change. He should convince them that he is truly interested and sincere in his wish for them to call. In the beginning, this may require a few night or weekend calls, but as the years progress these will diminish, and the patients will grow respectful of their doctor's time.

It is hard for many physicians to realize what an important figure they are to affective disorder patients. Because of the patient's surface competency and normality, the physician underestimates the patient's dependency and need for a consistent, professional caring figure. For a patient with affective disorder, a good physician is next to God; the physician should accept this role no matter how ludicrous it may appear.

It is important to remember also that the establishment of the therapeutic relationship must last for an extended period. The patient's denial is often strong in the beginning. He cannot accept that he has a chronic illness. The physician, too, may not wish to accept it. All of us have a wish that life's troubles will disappear and not return. With careful diagnosis, however, the physician establishes the nature of the recurrent disorder. Then he commits himself to objective treatment and long-term follow up.

## CONCLUSION

We cannot know with certainty the internal human process which fosters the doctor-patient relationship for affective disorder patients. However, it appears to the authors that the success of treatment depends not only on the skill of the medication regimen, but also on how well the patient is able to internalize the thinking and the concerns of the physician. The "good" patient appears to carry his physician with him everywhere. The good physician accepts this role as a necessary condition of treatment.

In the next article, we will incorporate these principles into the methodology of prescription of psychotropic medication.

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## FREE PERFORATION OF THE JEJUNUM IN CROHN'S DISEASE — Continued from Page 354

involved in the granulomatous process. As more precise medical management and a prolonged life expectancy of patients with regional enteritis occurs, it must be expected that the incidence of jejunal involvement will increase. Steroids and immunosuppressive therapy may lead to an increased incidence since these regimens may mask the severity of symptoms.

## SUMMARY

It has been noted that acute jejunal perforation is a rare entity. The above case is reported because of its unusual presentation and because only one other case of jejunal perforation due to an acute, previously unsuspected process, has been reported. Perforation may not always present with free air

under the diaphragm but must be suspected in a patient with a previous diagnosis of regional enteritis. Perforation due to Crohn's disease should be considered in the differential diagnosis when severe abdominal pain presents as an acute process.

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# Quadriparesis as an Unusual Manifestation of Hypercalcemia

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## ABSTRACT

**Quadriparesis as the presenting complaint in hypercalcemia has never been reported. This paper reports two patients in whom quadriparesis was the predominant manifestation of a hypercalcemic state.**

Hypercalcemia can produce bizarre, puzzling and confusing symptoms of such a diffuse nature that the patient may be thought to have a functional illness. The most common symptoms include fatigue, weakness, lethargy, constipation, nausea, anorexia and depression. Many patients with mild hypercalcemia are asymptomatic as we have found now that the SMA 12/60 gives us a read out for calcium.

Hypocalcemia is known to cause neuromuscular symptoms as well. The most common symptom is tetany with cramping and muscle irritability. Knapp and Gough<sup>1</sup> have reported three patients with weakness and signs suggestive of spinal cord compression. These patients had signs of posterior cord involvement and urinary incontinence or retention. This type of presentation has not been reported in hypercalcemia but the following cases demonstrate that calcium can be the culprit whether it is too high or too low.

## CASE REPORTS

E. S. was a 43-year-old Black female admitted to Metropolitan Hospital, New York Medical College on 10/8/69. Her original admission was to the Urology Service because she entered with the complaint of sudden onset of sharp crampy pain in the suprapubic region with radiation into the left thigh. She complained of weakness in her legs but both the patient and admitting physician attributed this to pain. Other history included amenorrhea for seven months and heavy intake of alcohol for five years. On examination she was obese, lethargic and had "clouded sensorium." BP was 140/90, pulse 108 and regular, temperature was 98.6 (37°C). Her neck was supple; her abdomen was obese but except for her neurologic signs the remainder of the physical examination was normal. Neurologically she was found to be unable to move her left lower extremity. There was slight atrophy of the left calf and there was no tenderness on palpation. She had bilateral hyperreflexia, bilateral Babinski's and was incontinent of both urine and feces. A lumbar puncture, myelogram and radionuclide scan were all within normal limits. Her EEG was abnormal and was characterized by generalized 5-6 cps activity. An echoencephalogram showed no mid line shift. It was felt that the patient had a transverse myelitis secondary to a viral infection and was treated with Decadron® over a five-day period. Laboratory studies on admission did not include calcium determinations. The patient improved considerably on steroids and was able to walk and control bladder and bowel function. On 11/3/77, because hepatomegaly had been noted on a follow-up examination, a "liver profile" was performed. Calcium at that time was 13.6 mg%. Over the next few days she again became lethargic and

weak. She rapidly progressed to coma and a repeat calcium was 17 mg%. She was treated with phosphates by nasogastric tube and a one dose intravenous solution of sodium sulfate. As her calcium decreased she became symptomatically improved. A cause of her calcium rise was sought but not found. The patient developed a bleeding diathesis and expired two months after admission. An autopsy was refused by the family.

A. P. is a 47-year-old Black female who was well until December of 1971 when she was admitted to Perth Amboy Hospital in New Jersey with severe low back pain. She had a myelogram during that admission and reportedly developed left hemiparesis following the procedure. In May of 1972, she was again admitted to PAH because of headache. She was found to be hypercalcemic and underwent a neck dissection which revealed normal parathyroids. Postoperatively she developed some weakness of the right upper extremity. In August 1972, the patient was admitted because of increasing weakness in both upper and lower extremities. On admission she was found to have normal vital signs. She was diffusely weak and had bilateral sustained ankle clonus. She was found to have an anemia of iron deficiency. Lumbar puncture was performed revealing a protein of 85 mg% with 4 WBC's. Her calcium ranged from 10 to 14 mg. EEG, brain scan and skull x-rays were normal. Because the patient was thought to have a neuromuscular disorder, she was transferred to the Columbia Presbyterian Medical Center, Neurological Institute. On admission at NI, the patient was found to be quadraparetic with a sensory level at approximately C2. The patient was lethargic and had difficulty cooperating. EEG's were repeated, two being reported as normal and the third showing rhythmic slowing. Nerve conduction and electromyographic studies were compatible with a polyneuropathy. A muscle biopsy indicated skeletal muscle atrophy of neurogenic type. A myelogram was essentially normal up to the clivus. Numerous laboratory studies were carried out with positive results including elevation of serum calcium, renal calculus in the upper pole of the right kidney, positive serology (the patient had a history of adequate treatment in the past) and positive PPD. Numerous other studies were not able to identify neoplastic or infectious disease. Her hypercalcemia was treated with intermittent phospho soda by mouth. As her calcium responded to therapy, she showed progressive increase in strength. She also had gradual return of sensation. She lost her Babinski reflexes and regained bowel and bladder control. She retained clonus in the right ankle.

It was felt that she probably had either a parathyroid adenoma or a parathormone secreting neoplasm. No source of neoplasm was located and a neck dissection was recommended but refused by the patient who was discharged to home on phospho soda 10cc TID.

Primary hyperparathyroidism, either as a result of tumor or hyperplasia of the parathyroid glands, is the most common cause of hypercalcemia. Hypovitaminosis D, multiple myelomatosis, metastatic malignancy and milk-alkali syndrome are other less common causes. The advent of automated serum chemical determinations has made us aware of another entity that of asymptomatic hypercalcemia.

The effect of an increase in circulating parathyroid hormone is to increase excretion of phosphorus by the kidney, lowering the serum phosphorus and causing a compensatory rise in calcium

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to maintain ionic balance. The calcium rise is usually at the expense of the bones. Neurological symptoms in chronic cases include headache, weakness and anxiety. A proximal myopathy has been described in hyperparathyroidism, not necessarily in association with hypercalcemia (Vicale<sup>2</sup>). The patient may complain of easy fatigue and muscle cramps and pains. Bischoff and Esslen<sup>3</sup> have described EMG changes suggestive of myopathy without fibrillation potentials to suggest denervation.

Calcium is essential to membrane integrity and function. If calcium concentration is higher than normal there is a decrease in neuromuscular transmission. Hypotonia of all muscles results giving rise to complaints of weakness. Smooth muscle is also involved which would explain constipation and urinary retention. Involvement of cardiac muscle can shorten the QT interval. Hypocalcemia can, in extreme cases cause very similar neuromuscular changes. Initial decrease in calcium concentration causes hyperexcitability but as calcium decreases, transmission of impulses may be blocked completely.

The patients described each had at least one abnormal EEG. EEG changes in hypercalcemia have been reported by several authors including Cohn and Sode<sup>4</sup> and Allen, et al.<sup>5</sup> These changes are usually related to the calcium level, including generalized slowing with excessive amounts of theta and delta ranged activity as well as high voltage bilaterally synchronous slowing. The slow wave activity generally returns to normal sometimes over a period of several weeks and not as a reflection of changes in the serum calcium. Neuromuscular symptoms cleared as the calcium levels declined

indicating that there is no structural change in the neuromuscular junctions.

Treatment of the hypercalcemic state includes restriction of calcium intake, hydration, saline infusion, and use of a diuretic-like furosemide. The patient should be kept mobile since immobility increases the calcium loss from bone. Steroids, used almost accidentally in the first case will help to lower serum calcium in patients with myeloma, sarcoidosis, vitamin D intoxication and in some patients with breast carcinoma. A recent addition to treatment available is dialysis. Mithramycin has been recommended especially in patients with hypercalcemia in association with metastatic carcinoma. Sodium sulfate may be given intravenously instead of sodium chloride. Oral phosphates may be useful although in a patient with vomiting, diarrhea, or coma its usefulness is limited. Phosphates in themselves can cause diarrhea.

Effective treatment of hypercalcemia begins with diagnosis. Realizing that hyper or hypocalcemia may present with unusual neurological manifestation including a picture simulating transverse myelitis or a cord lesion, will eliminate time spent in unproductive studies.

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#### A METHOD FOR IMPROVING THE USE OF CONSTANT INFUSION DRUGS IN CARDIOTHORACIC PATIENTS

*Continued from Page 362*

to allow one to pick an adequate dose of drug without excessive fluid administration. By the simple expedient of making a drug solution based on the patient's weight (mcg/kg/ml), drug dose tables can be used which indicate the drug dose in micrograms per kilogram per minute (mcg/kg/min) when the hourly infusion rate is known.

of the IV rate-drug dose tables together with appropriate weight multiplication factors for dopamine, nitroprusside, nitroglycerin, and epinephrine.

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Footnote: We will gladly furnish to interested persons copies

# Missed Appointments in Maine Medical Center's Outpatient Department

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The efficient delivery of medical care in the Outpatient Department of the Maine Medical Center (MMC), like that of many other urban hospital-based clinics, is disrupted by problems of patient non-compliance. The broken appointment rate, which averages 25%, has caused particular concern. A patient who breaks an appointment receives less than optimal care as assessed by the professional who scheduled that visit. Moreover, the misallocation of staff and time caused by missed appointments contributes to the clinic's financial deficit.

Studies of appointment breaking in various ambulatory systems, such as pediatric clinics, orthopedic clinics, general medical clinics, and group practices, show failure rates of 15 to 44 percent.<sup>1,2,11,12,17</sup> A number of variables which influence the rate of broken appointments have been identified. They include the availability and accessibility of care (the physical location and time of clinics),<sup>1</sup> the clinic philosophy (staff-patient relationships),<sup>1,5,10</sup> patient attitudes (perceptions regarding the quality of care being delivered and the desirability of obtaining the proper care)<sup>1,5</sup> and socioeconomic and demographic factors.<sup>1,2,5,10,11,15</sup>

While recognizing the importance of all of the above variables, a study of "selected patient characteristics" was deemed to be most productive in the evaluation of the MMC's Outpatient Department no show rate.

## METHODS

### *Setting*

The general medical clinic, the largest of the outpatient clinics at the Maine Medical Center, has a volume of 7,000 visits per year and 25-30 patients per session. At the time of the study, each session was staffed by four physicians, including interns, residents, and private practitioners, as well as three or more nurses. One nurse served as the triage coordinator to assist the walk-in patient. One or two secretaries answered phones, scheduled appointments, and responded to patient inquiries.

Appointments were scheduled for one-half hour for return patients and one hour during the first hour of the clinic was reserved for initial medical work-

ups. Should a patient fail to appear, the head nurse would call the patient and rebook the appointment for the next convenient session.

Entrance into the clinic did not depend on the fulfillment of special requirements and was either patient initiated or via referral from sources which included the emergency department, other outpatient clinics, agencies, or private physicians.

### *Data Collection*

A comprehensive record review was performed to gather data. A coding form was developed specifically to test the *a priori* hypothesis. The questions were divided into three sets: 1) demographic make-up of the study population; 2) utilization of MMC services; and 3) patient's physical condition. The first set included age, sex, marital status, address changes, occupation and method of payment codes. The second set dealt with the patient's prior contact with the clinic, the doctors, and other MMC departments. The final set covered the patient's major diagnoses and medications.

The appointment list of patients for the month of June 1974 provided a population of 687 patients. Names, chart numbers, and appointment dates were recorded from the appointment book. Repeat visits by a single patient were discarded so that patients, not visits, constituted the study population. Using a table of random numbers, a sample of 150 patients were drawn. Because six charts were unavailable or incomplete, there were 144 usable charts.

## RESULTS

### *Patient Demographics*

As expected, older patients complied more often with scheduled appointments. Table 1 illustrates a strikingly disproportionate rate of no shows in the 15 to 24 age group. The best show rate is in the 25 to 44 age bracket. Although other studies suggested that females would be more likely to keep appointments, no difference was found in the rates for males and for females.

Marital status was related to the rate of appointment breaking (See Table 2). Married and widowed patients were more likely to keep their appointments. Divorced and single patients had twice the no show rate. Part of the finding may be confounded by the age difference of the populations since the single group is younger than the others.

Although it had been hypothesized that patients receiving totally free or partially free care would

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TABLE 1

AGE DISTRIBUTION			
AGE	Total Population	Number of No-Shows	Percent of No-Shows
0-14	0	0	0
15-24	10	4	40
25-44	25	5	20
45-64	53	13	24
65+	48	13	27
Unknown	8	2	25
TOTAL	144	37	26

TABLE 2

MARITAL STATUS			
	Total Population	Number of No-Shows	Percent of No-Shows
Single	23	9	39
Married	59	10	17
Divorced	21	9	43
Widowed	33	7	21
Unknown	8	2	25
TOTAL	144	37	26

TABLE 3

SOURCE OF PAYMENT			
Source	Total Population	Number of No-Shows	Percent of No-Shows
Pt. Pays	18	4	22
3rd Party			
Pt. Pays			
½ Balance	38	11	29
3rd Party,			
Balance Free	57	13	23
Free	23	7	30
Unknown	8	2	25
TOTAL	144	37	26

TABLE 4

OCCUPATION			
Occupation	Total Population	Number of No-Shows	Percent of No-Shows
Unemployed	38	14	37
Unskilled Labor	13	3	23
Retired/Soc. Sec.	58	13	22
Other (skilled clerical, agri.)	22	5	23
Unknown	13	2	15
TOTAL	144	37	26

exhibit a higher no show rate, there appeared to be no significant correlation between the method of payment and the no show rate (Table 3).

Occupational status of the patient, however, is related to appointment keeping. Unemployed individuals are most likely to miss appointments (See Table 4).

Table 5 presents the rate of appointment failures according to distance from the clinic. A patient residing outside of the Greater Portland area is more likely to keep a scheduled appointment. The data in Table 6 show that residential instability affects the rate of broken appointments. Thirty-two percent of the patients with one or more recorded changes of

TABLE 5

DISTANCE FROM THE CLINIC			
Residence	Total Population	Number of No-Shows	Percent of No-Shows
Portland	83	26	31
UCS*	31	8	26
Other	29	3	10
Unknown	1	0	0
TOTAL	144	37	26

\*UCS Towns include: South Portland, Scarborough, Cape Elizabeth, Falmouth, Cumberland, Yarmouth, North Yarmouth, Windham, Gorham, Westbrook, and Freeport.

TABLE 6

NUMBER OF ADDRESS CHANGES			
Number	Total Population	Number of No-Shows	Percent of No-Shows
No Change	61	12	20
One or More	73	23	32
Unknown	10	2	20
TOTAL	144	37	26

TABLE 7

RATES FOR NEW AND RETURNING PATIENTS			
Status	Total Population	Number of No-Shows	Percent of No-Shows
New	20	2	10
Returning	124	35	28
TOTAL	144	37	26

TABLE 8

LENGTH OF TIME KNOWN TO CLINIC			
Time	Total Population	Number of No-Shows	Percent of No-Shows
No Previous Visits	18	2	11
0-12 Months	31	12	39
12-24 Months	12	2	17
24-60 Months	16	3	19
60+	59	18	30
Unknown	8	—	—
TOTAL	144	37	26

address missed appointments. Only 20 percent of those with no changes failed appear.

#### Utilization of MMC Services

Ninety percent of all new patients and 72 percent of the returning patients in the study population kept their appointments (See Table 7).

Table 8 shows that the length of time that a patient is known to the clinic is also related to compliance with scheduled appointments. Patients who have attended the clinic for less than one year or more than five years have a greater tendency to miss appointments.

In the general medical clinic, the 37 no show patients had an average of 2.16 broken appointments during two years, while the show population averaged .98 broken appointments. Patients who habitually failed to keep scheduled appointments also

tended to use the emergency department to a greater extent. The 37 appointment breakers accumulated a total of 174 emergency department visits in the preceding five-year period for an average of 4.14 visits per patient. Patients keeping appointments made 264 or 2.47 visits per patient. Moreover, the 37 no show patients in this medical clinic study compiled an average of 3.2 broken appointments in *all* clinics during the same two years. During this same period, the show population missed appointments at the rate of 1.7.

Previous hospitalization at the MMC appears to have little effect on compliance with scheduled visits. Twenty-eight percent of those missing appointments had been hospitalized and 23 percent had not.

Continuity of physician contact did, as anticipated, improve the show rate. Only thirty percent of the patients breaking appointments had seen the same physician on three previous visits. Of those keeping appointments, 54 percent had been treated three times by the same physicians.

### *Patient's Condition*

Our study showed no significant difference between the no show and show populations with respect to the number of active problems or the number of active medications. However, 19 of 37, or 51 percent of the appointment breakers had a psychiatric diagnosis listed as a major problem. Psychiatric disorders were diagnosed in 35 percent (37 of 107) of the show population.

### **DISCUSSION**

This study indicated that it is possible to characterize the appointment breaking population in the general medical clinic of the Maine Medical Center.

Return patients from Portland in the young adult age bracket (15 to 25 years of age) had the highest proportion of no shows. Patients without spouses, either single or divorced, failed a significantly higher number of appointments than married patients. The relationship of marital status to age, which was not explored, might account in part for the higher failure rates among unmarried individuals but could not explain the total difference. Other studies of patient characteristics have shown varied results with regard to the age of appointment breakers. Several reports found that, in an urban setting, age in conjunction with race correlates with a high broken appointment rate.<sup>2,11,18</sup> In cases, young, non-whites had the highest failure rates. Young adults also demonstrated a higher failure rate in a study undertaken by Hurtado.<sup>10</sup>

As in several earlier studies<sup>11,17,18</sup> sex of the patient and method of payment did not correlate with the tendency to break appointments. The number of problems and/or medications and previous hospitalization at the Maine Medical Center bear no relationship to non-compliance with scheduled appointments. However, a psychiatric diagnosis was

present more often among appointment breakers. Alpert<sup>1</sup> has also noted more psychiatric problems in the no show population.

An unemployed status and residential instability, both characteristics of low socio-economic state, correlated with appointment breaking. According to Alpert<sup>1</sup> and to Badgley and Furnal,<sup>2</sup> low socio-economic status is associated with appointment failures.

Failure to provide physician continuity also resulted in a moderately high no show rate. Similar findings have been reported by Hansen,<sup>9</sup> Alpert,<sup>1</sup> and Hurtado.<sup>10</sup> However, Olencki and Reader<sup>18</sup> found that a continuing relationship with one physician was not a factor in appointment failures.

Appointment breaking by the no show population is not a random occurrence. This group had twice the number of missed appointments in the specific clinic and in all the other clinics at the Maine Medical Center. In addition, appointment breakers used the Emergency Division at twice the rate of the keepers.

### **SUMMARY**

This study was undertaken to identify the significant demographic and behavioral characteristics of patients who fail to comply with scheduled appointments in the general medical clinic of the Maine Medical Center.

Appointment breaking was found to correlate with age, proximity to the clinics, marital status, residential instability, physician continuity, and the time known to the clinic. Sex, method of payment, previous hospitalization and the number of active problems or medications bore no relationship to appointment failures.

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# To IPPB or Not to IPPB

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Intermittent positive pressure breathing (IPPB) has undergone large changes in popularity. Most recently there have been a number of papers criticizing the widespread use of IPPB and suggesting that it is overused.<sup>1-4</sup> It is the purpose of this paper to review the status of IPPB on the basis of what is known from the literature and to try to arrive at a rational approach to its use. We are referring solely to the use of positive pressure breathing apparatus in a non-intubated patient and not considering the use of positive pressure ventilation for support of an intubated patient in respiratory failure.

It is not fashionable to use IPPB at the present time. A number of articles criticize the current use of IPPB.<sup>1-5</sup> Statistics from various Maine hospitals recently demonstrate that the use of IPPB has fallen off significantly in the last 2-3 years, and in one southern Maine hospital it has disappeared almost completely.<sup>6</sup> This has happened without any new therapy supplanting IPPB and with no significant new evidence appearing in the literature to support this change in usage. We think it is important to examine the causes for this apparent change in fashion. We first will delineate those indications for which IPPB is of (1) proven value, (2) uncertain value and (3) no value. We will then review what we consider a reasonable approach to the use of IPPB.

## IPPB OF PROVEN VALUE

Racemic epinephrine delivered via an IPPB machine to children with infectious croup and with laryngeal edema after intubation has clearly been shown to be efficacious.<sup>7,8</sup> No other form of therapy has been as effective in forestalling intubation or re-intubation of these patients. Some of the early articles suggested that one could forestall hospitalization by use of this as an outpatient treatment. More recent studies, however, strongly suggest that these patients be hospitalized for observation.

There have been a number of papers that were unable to demonstrate any benefit from IPPB compared to other methods in delivering inhaled bronchodilator in COPD.<sup>9-13</sup> However, Choo-Kang and Grant demonstrated a benefit of Salbutamol delivered by IPPB over Salbutamol delivered by a pressurized canister.<sup>14</sup> The advantage of IPPB over the pressurized canister was greatest for the most obstructed patients and decreased proportionately

as the patient's disease became less severe. In the group with the best FEV<sub>1</sub> (greater than 2.0) there was no difference between the IPPB delivered and canister delivered bronchodilator. A similar study comparing IPPB to other nebulizers delivering Salbutamol has not been done.

## IPPB OF UNCERTAIN VALUE

There are a number of studies in the literature which mention that no objective changes have been measured in patients treated with IPPB versus patients treated in identical manner except without IPPB.<sup>9-13</sup> Most, if not all, of these studies end with a statement to the effect that "patients state that IPPB helps open air passages and increases sputum." The question then becomes, are we dealing with placebo effect or are we not measuring the pertinent variables. Pulmonary medicine is replete with studies where the subjective data is more sensitive or specific than objective data.<sup>15,16</sup> Since it is impossible to do a double blind study on IPPB, we may never have a satisfactory answer to this question.

Several studies have demonstrated that one can transiently lower the PCO<sub>2</sub> with IPPB.<sup>17</sup> In addition, the work of breathing can be lowered by the use of IPPB. Oxygen uptake was decreased by 6 percent during IPPB treatment in one study.<sup>18</sup> In normal human beings, the oxygen uptake due to the respiratory muscles is no more than 2 percent of total; this may rise to 30 percent in severe COPD. A reduction in oxygen uptake of 6 percent due to respiratory assistance suggests a marked decrease in respiratory effort. Other studies, however, show an increase in airway resistance which would tend to increase work of breathing after a treatment.<sup>17,18,19,20</sup>

A number of studies have suggested that in post-operative patients IPPB is no better or worse than other modes of therapy which require the patient to take a deep breath and/or cough.<sup>21,22</sup> Attention to pulmonary hygiene in the postoperative situation is associated with a decreased incidence of atelectasis and pneumonia. One study demonstrates that IPPB is equal to blow bottles and that both are superior to no therapy in the prevention and treatment of post-operative atelectasis.<sup>22</sup> The benefit is more apparent in patients with known lung disease and in smokers than in non-smokers without lung disease. To date it is not known whether IPPB is more or less expensive than other equally efficacious methods nor is it known which has the higher risks of adverse effects. We do not know the optimum length of treatment with IPPB, the optimum length or type of chest physical therapy treatment or the optimum length of time for a nurse to spend with a patient instructing him to breathe deeply and cough forcefully. Until

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basic data such as that is available, true estimates of cost effectiveness will not be possible.

Mucolytic agents delivered by IPPB are probably of benefit in patients with cystic fibrosis. They are probably contraindicated in all other patients and should never be used without a concomitant bronchodilator. Some physicians feel IPPB is contraindicated in cystic fibrosis because of the risk of pneumothorax.

#### IPPB OF NO VALUE

Finally, there are a number of instances where the use of IPPB is clearly not indicated. For example, there is little rationale and no empiric data to support the use of out-patient IPPB three times a week. There may be some obstructed patients in whom home IPPB for the delivery of bronchodilators is rational, but there does not seem to be any excuse for "puff parlors" except to make money. Similarly, it probably is not rational to use IPPB without bronchodilator in every post-op patient. Which, if any, post-op patients need IPPB is still a matter of conjecture.

#### RISKS

The risks of IPPB must be considered when considering its benefits. Depression of cardiac output has been a theoretic and physiologic measured complication of IPPB; however, we know of no instance where this was clinically significant in a patient not on a ventilator. There is said to be a risk of pneumothorax,<sup>23</sup> although again this is very rare. An important and well documented complication of IPPB therapy may be the spread of organisms by contaminated or improperly cleaned equipment. This has been much less frequent as therapists have become aware of its potential complication.

In summary, IPPB is currently not fashionable. Nevertheless, there are certain indications for which it is the treatment of choice and other indications for which it has been demonstrated to be equal to other modes of therapy. It undoubtedly is being overused in many areas although its use varies widely over the entire State of Maine.

#### GUIDELINES FOR USE OF IPPB

In the face of a very few clear-cut indications for IPPB, a number of non-indications for the use of IPPB, and a large grey area in-between, it is difficult to arrive at a set of guidelines that will be acceptable to a majority of physicians. Our personal viewpoint is that IPPB with racemic epinephrine is the treatment of choice for upper airway obstruction particularly when edema is a major factor. We frequently use IPPB for the delivery of bronchodilators in severely obstructed ill patients with known bronchoreactive disease. Almost invariably we transfer these patients to inhaled bronchodilators via Freon propellant canisters or other nebulizers when they become ambulatory and/or less severely obstructed. Rare patients remain on IPPB or other

compressed air powered nebulizers. We use IPPB (without alcohol) in the treatment of acutely dyspneic patients with pulmonary edema. We also use it for the prevention of atelectasis in patients with acute neuromuscular disease such as Guillain-Barre. The rationale for these latter two uses in the literature is essentially non-existent. In selected patients, usually those with chronic obstructive lung disease with significant postoperative atelectasis, we use IPPB with a bronchodilator in conjunction with vigorous chest physical therapy and early ambulation. In patients with no known lung disease we feel frequent reminders to cough and deep breathe by the nursing staff and early ambulation is adequate for the prevention of atelectasis. IPPB as the only attention to a patients respiratory status postoperative does not seem rational. While we recognize that in certain institutions this may be the only mechanism by which a physician can assure his patient will have someone paying attention to his respiratory status, we do not feel this is rational and would suggest such hospitals develop mechanisms by which less expensive and potentially less dangerous maneuvers such as coughing and deep breathing be made readily available. There are, therefore, few indications for IPPB without bronchodilators and we do not feel IPPB should be used except as a portion of an integrated program of respiratory care.

#### SUMMARY

IPPB is useful in the delivery of racemic epinephrine for an upper airway obstruction secondary to croup or laryngeal edema. It is one effective method of delivery of inhaled bronchodilators. It may be useful in pulmonary edema secondary to left ventricular failure, and it is logical to use in treating or preventing atelectasis in patients with neuromuscular weakness. Its use in delivery of an aerosol still needs adequate comparison to other techniques. Likewise, there is no evidence that it is more effective in treating postoperative atelectasis than deep breathing and chest physical therapy alone. Intermittent outpatient use is clearly not beneficial, and should be avoided as an unnecessary expense.

#### ACKNOWLEDGMENT

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# Diagnostic Approach to a Pleural Effusion

IRVIN L. PARADIS, M.D.\* and EDGAR J. CALDWELL, M.D.\*\*

## INTRODUCTION

Fluid in the pleural space remains a common diagnostic problem. Even though the cause of the effusion may seem obvious, any fluid in the pleural space requires analysis as it may represent an apparent serious disease. Properly handled fluid and/or tissue will usually yield the diagnosis, although in a small number of instances the cause may remain unknown.

This paper reviews the mechanisms relating to pleural fluid formation and compares the results obtained in pleural fluid analysis at the Maine Medical Center to similar studies at the Mayo Clinic<sup>1</sup> and Johns Hopkins Hospital.<sup>3</sup> By providing recommendations on the proper handling and on the studies to perform on pleural fluid, this paper provides a logical approach to the diagnosis of a pleural effusion.

## PHYSIOLOGY

The pleural space is lined by parietal and visceral membranes which are permeable to liquid and gas. In normals, the space may contain a small amount of liquid (up to 15 cc) but no gas. In intrathoracic disease or as a result of systemic disease, large quantities of fluid may accumulate in the pleural space. In the following equation, Starling described the forces that determine bulk movement of water between vascular and extravascular compartments.

$$FM = K (HP_C - HP_{IF}) - (COP_C - COP_{IF})$$

Fluid movement (FM) results from an imbalance between filtration and reabsorption forces. The components of the equation are defined below with mean normal values in parentheses:

- K = filtration co-efficient which is a measure of permeability of a capillary wall to fluid
- HP<sub>CP</sub> = capillary hydrostatic pressure of parietal pleura (30 cm H<sub>2</sub>O)
- HP<sub>CV</sub> = capillary hydrostatic pressure of visceral pleura (11 cm H<sub>2</sub>O)
- HP<sub>IF</sub> = interstitial or intrapleural hydrostatic pressure (-5 cm H<sub>2</sub>O)
- COP<sub>C</sub> = capillary or plasma oncotic pressure (32 cm H<sub>2</sub>O)
- COP<sub>IF</sub> = interstitial or pleural fluid oncotic pressure (6 cm H<sub>2</sub>O)

The normal values in parentheses can be substituted into the Starling equation to illustrate the sum of forces acting on the tissues which determine fluid

flow. The parietal pleura is supplied by the systemic arterial pressure system and the visceral pleura by the pulmonary arterial system; therefore, there is a much higher capillary hydrostatic pressure in the parietal pleura. The net movement of fluid is then from parietal pleura, across the pleural space, and through the visceral pleura.

At the level of the parietal pleural capillary, there is a net driving pressure (P<sub>D</sub>) of 9 cm H<sub>2</sub>O which tends to drive fluid into the pleural space.

$$P_{DP} = (HP_{CP} - HP_{IF}) - (COP_C - COP_{IF})$$

$$P_{DP} = (30 - -5) - (32 - 6)$$

$$P_{DP} = 9 \text{ cm H}_2\text{O}$$

At the level of the visceral pleural capillary, there is a net driving pressure of -10 cm H<sub>2</sub>O which tends to drive fluid from the pleural space into the visceral pleural capillary.

$$P_{DV} = (HP_{CV} - HP_{IF}) - (COP_C - COP_{IF})$$

$$P_{DV} = (11 - -5) - (32 - 6)$$

$$P_{DV} = 10 \text{ cm H}_2\text{O}$$

Therefore, under normal conditions there is a net driving pressure of 19 cm H<sub>2</sub>O causing fluid to be filtered out of the parietal pleural capillaries and absorbed by the visceral pleural capillaries. The components of the Starling equation can be altered by local or systemic disease which result in the accumulation of a pleural effusion.

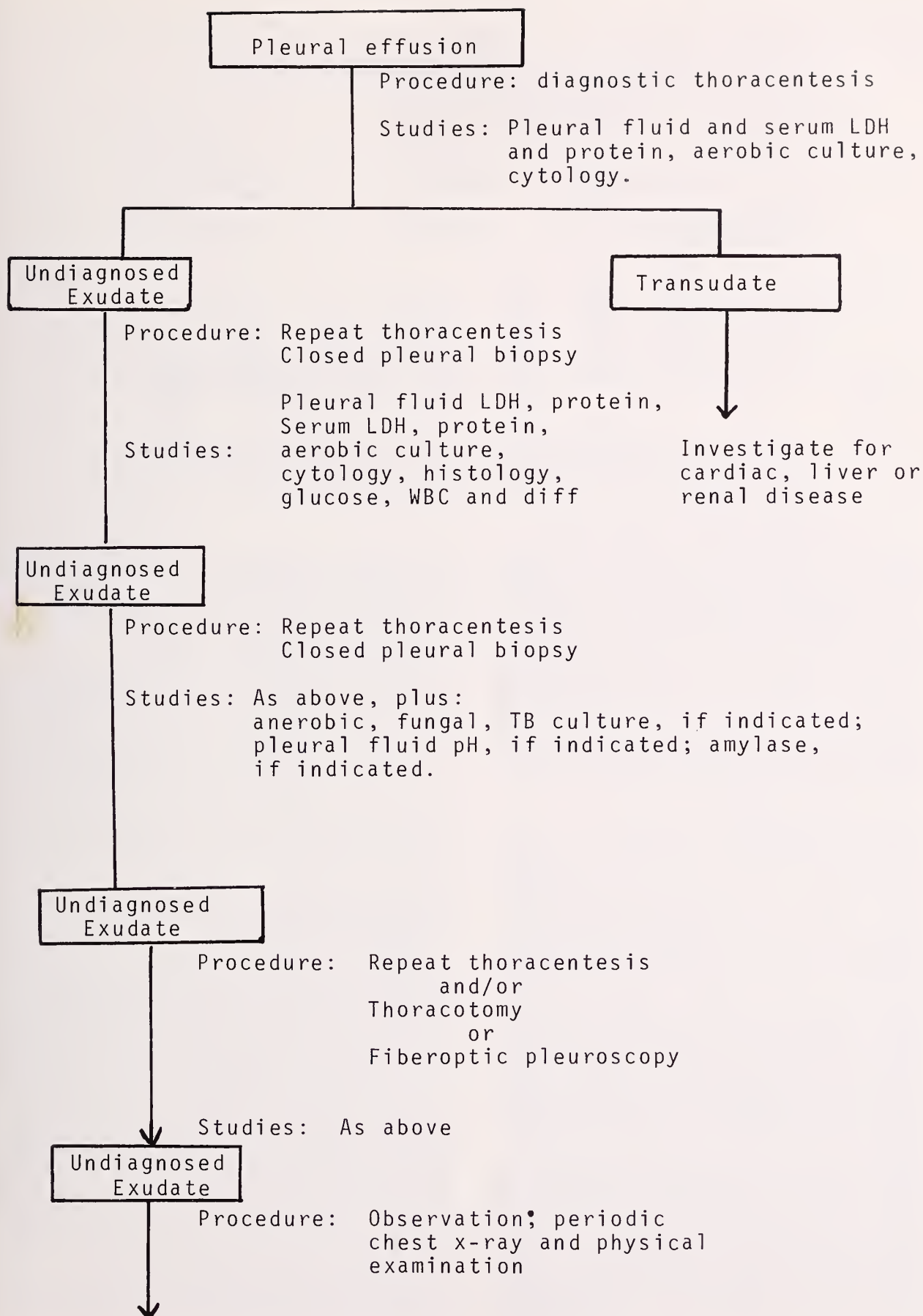
## METHODS

This study was based on the review of the charts of 96 patients with pleural effusion who were hospitalized at the Maine Medical Center during 1975 and 1976. The criteria defining the particular disease causing a pleural effusion are listed below. They are identical to those used in the Hopkins study.<sup>3</sup> The diagnosis of a malignant effusion required that malignant tissue or cells be shown by pleural biopsy or cytopathology. The diagnosis of tuberculous pleuritis required either 1) mycobacterium tuberculosis cultured from pleural fluid or tissue, or 2) granulomas on pleural biopsy. The diagnosis of pneumonia with effusion required that there be an acute febrile illness, with purulent sputum and pulmonary infiltrates, in association with a unilateral pleural effusion unaccompanied by clinical signs of congestive heart failure. The diagnosis of congestive heart failure as the cause of the pleural effusion required that all four of the following criteria be satisfied: 1) an enlarged heart; 2) an elevated central venous pressure or distended neck veins and pitting edema or ventricular cardiac gallop; 3) the absence of pulmonary infiltrates, purulent sputum, thrombophlebitis and pleuritic chest pain; and 4) clearing of the effusion in response to a therapeutic cardiac regimen.

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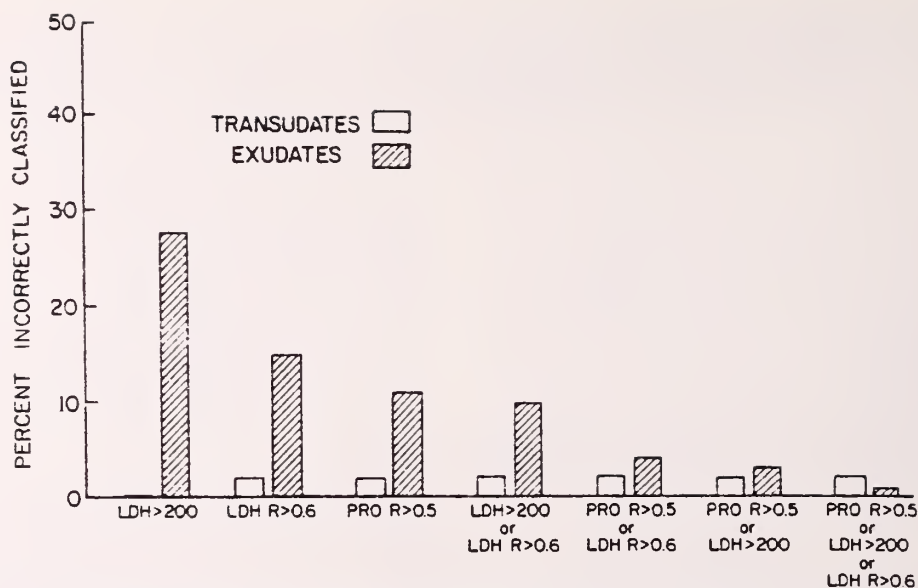


Fig. 1: The percentage of false-negative exudates and false-positive transudates by using various criteria. A fluid was classified as an exudate if it had the characteristic protein ratio (PRO R) and the lactic dehydrogenase (LDH) level or LDH ratio (LDH R) or both, listed at the bottom of the figure.

In interpreting the results of Table 2 and Figure 1, a positive result occurs when the observed pleural fluid values are consistent with an exudate in a patient with a pleural disease expected to cause an exudate. Thus, a false-negative result occurs when the observed pleural fluid values are consistent with a transudate in a patient with a pleural disease expected to cause an exudate. A false-positive result occurs when the observed pleural fluid values are consistent with an exudate in a patient with a pleural disease expected to cause a transudate.

### RESULTS AND DISCUSSION

Overall results (Table 1) indicate that of 96 patients at the Maine Medical Center (MMC) with a pleural effusion, 72 thoracenteses were performed; 24 patients did not have a thoracentesis. In the other studies, all patients had at least one thoracentesis. Thirteen of 72 patients at the MMC had therapeutic thoracenteses and therefore no studies were performed on the fluid. This is similar to the Mayo Clinic experience. Altogether, the 37 patients on whom no pleural fluid was obtained or studied is considerably higher than the Mayo Clinic. A definitive diagnosis was made on 61% of the 59 patients whose fluid was studied. This is comparable to the Mayo study, but both are lower than the Hopkins study.

Initial evaluation of a pleural fluid should determine whether it is an exudate or transudate. The distinction between a transudate and exudate relies on measuring the total protein and LDH in the pleural fluid and serum simultaneously. In addition to the absolute values of pleural fluid protein and LDH, the ratio of each of these to their corresponding serum value can be determined. The ability of

each of these measurements to be consistent with the patients underlying disease can be assessed by comparing each value with the etiology of the patients pleural effusion as determined by the previously mentioned criteria (Methods).

Table 2 identifies the four criteria which have been used to distinguish transudates from exudates. This table demonstrates the percentage of false-positive and false-negative measurements when each criteria is used as the sole indicator of whether a fluid is a transudate or exudate. It compares the data obtained from the MMC study to the Johns Hopkins study. They reviewed the false-positive and false-negative rate for each of these individual determinates. Since the etiology of every pleural effusion was definitely known, the individual measurements were correlated with the diagnostic category of the pleural disease.

These four criteria yield about a 10% false-negative and about 1% false-positive rate as seen in Table 2 and from the first three columns of Figure 1 which is reproduced from the work of Light, et al.<sup>3</sup> Columns 4, 5, 6 of this Figure demonstrate that the false-negative rate declines to about 5% when any pair or criteria correlate with the pleural effusion. Finally, when three variables are used simultaneously (Column 7), the likelihood of having a false-positive or false-negative pleural effusion falls to about 1%. This data can be summarized in Table 3 as the criteria for differentiating a pleural fluid as a transudate from an exudate. If all of these variables are in the same category, the patient will have that type of pleural disease 99 times out of 100.

Cultures of pleural fluid (Table 4) were the most frequently performed test with the lowest yield in both studies. This undoubtedly reflects clinical con-

TABLE 1

OVERALL RESULTS OF RETROSPECTIVE STUDY OF PLEURAL EFFUSIONS AT MMC AND MAYO CLINIC AND PROSPECTIVE STUDY OF SAME AT JOHNS HOPKINS			
	MMC	Mayo	Hopkins
Patients	96	133	150
Thoracentesis	72	204	188
Studies Ordered	59/72 (81%)	164/204 (80%)	188 (100%)
Studies Not Ordered	13/72 (19%)	40/204 (20%)	0
No Tap or No Studies	37/96 (39%)	40/204 (20%)	0
Diagnosis Made	36/59 (61%)	108/164 (66%)	150/188 (80%)
Diagnosis Not Made	23/59 (39%)	56/164 (34%)	33/188 (20%)

TABLE 2

NUMBER OF INDIVIDUAL MEASUREMENTS AT MMC AND HOPKINS ON SERUM AND PLEURAL FLUID OF PROTEIN AND LDH WITH FLUID AND SERUM, PROTEIN AND LDH EXPRESSED AS A RATIO. ALSO THE NUMBER OF FALSE-POSITIVE TRANSUDATES AND FALSE-NEGATIVE EXUDATES BASED ON EACH INDIVIDUAL VALUE

	MMC	Hopkins
I Protein	31/59 (53%)	150/150 (100%)
Less than 3 gms	9/31 (29%)	54/150 (36%)
More than 3 gms	22/31 (71%)	96/150 (64%)
Overall Error		
False-negative	3/9 (33%)	4/47 (8%)
False-positive	2/27 (7%)	11/103 (11%)
II Protein: Fluid/Serum Ratio		
Less than .5	8/31 (26%)	56/150 (37%)
More than .5	23/31 (74%)	94/150 (63%)
Overall Error		
False-negative	3/9 (33%)	1/47 (2%)
False-positive	1/27 (4%)	10/103 (10%)
III LDH	25/59 (42%)	150/150 (100%)
Less than 200	17/25 (68%)	77/150 (51%)
More than 200	8/25 (32%)	73/150 (49%)
Overall Error		
False-negative	0/9 (0%)	0/47 (0%)
False-positive	6/27 (22%)	30/103 (29%)
IV LDH: Fluid/Serum Ratio		
Less than .6	10/25 (40%)	
More than .6	15/25 (60%)	
Overall Error		
False-negative	1/9 (11%)	1/47 (2%)
False-positive	2/27 (7%)	14/103 (14%)

cern for not overlooking treatable but potentially devastating diseases such as empyema and tuberculosis. Empyema occurs by direct extension of infection into the pleural space from a pneumonia, or as a consequence of septicemia from a distant focus of infection. Recognition of an empyema has depended on the observation of purulent pleural fluid or the presence of organisms on smear or culture. This analysis is sometimes inaccurate and, in the case of cultures, there is a time lag.

Pleural effusions develop frequently during the course of bacterial pneumonias; most resolve spontaneously. A method for separating benign effusions from an empyema involves measuring the pleural fluid pH. A recent study<sup>2</sup> has shown that nearly all empyemas (90%) have a pH of less than 7.20 and no benign effusions have a pH of less than 7.30. The most important treatment of an empyema is adequate drainage. Current recommendations for a closed drainage procedure are: 1) presence of gross pus; 2) organisms on gram stain or culture; and 3)

TABLE 3

CRITERIA TO DEFINE A PLEURAL EFFUSION AS A TRANSUDATE OR EXUDATE

Chemistry of Pleural Effusions		
	Transudates	Exudates
Protein	< 3 gms	> 3 gms
Protein, Fluid/Serum Ratio	< .5	> .5
LDH	< 200	> 200
LDH, Fluid/Serum Ratio	< .6	> .6

TABLE 4

TOTAL NUMBERS OF CULTURED PLEURAL FLUIDS AND NUMBERS OF POSITIVE CULTURES

Cultures	MMC	Mayo	Hopkins
Total Cultures	53/59 (89%)	143/164 (87%)	
Aerobic	53/53 (100%)	127/143 (89%)	
Anerobic	UK	16/143 (11%)	
Positive Aerobic	5	4	
Positive Anerobic	1	1	
Positive Fungal	1	1/76	
Positive TB	0	1/103	

TABLE 5

CYTOLOGY AND PLEURAL BIOPSY RESULTS AT TWO INSTITUTIONS

	MMC	Mayo
Cytology	45/59 (76%)	136/164 (83%)
Positive	7/45 (16%)	20/136 (15%)
Biopsy	14/59 (24%)	28/164 (17%)
Malignant	1	8
Malignant and Pos. Cytology	1	6
Malignant and Neg. Cytology	0	2
Nondiagnostic	13	20
Nondiagnostic/Pos. Cytology	0	2
Pos. Biopsy in CA Patient	1/7 (15%)	8/20 (40%)

pleural fluid pH less than 7.20. To prevent falsely low measurements of pleural fluid pH due to continued metabolism of cells in the fluid, the specimen should be handled as an arterial blood gas: 1) collect specimen anaerobically; 2) use heparinized syringes; 3) transfer to laboratory in ice, and 4) measure pH as soon as possible. In interpreting the pleural fluid pH, the pleural fluid pH varies directly with systemic blood pH and must therefore be at least .15 units lower than a simultaneous arterial pH to be significant. Lastly, the use of the pleural fluid pH as a criteria for the placement of chest tubes is valid only with empyema or effusions associated with pneumonias.

Pleural fluid cytology (Table 5) was the second

most frequently performed test in both studies. The results are similar in both studies and indicate that cytopathology is more sensitive than pleural biopsy to detect carcinoma in the pleural space. Only 40% of the Mayo clinic patients with positive cytologies had a positive pleural biopsy (Table 5). However, two patients had a positive biopsy and negative cytology. In an effusion of long-standing duration, the pleural fluid cytology may be difficult to interpret. In this situation, repeat thoracentesis of newly re-accumulated pleural fluid will frequently yield positive results.

To evaluate the diagnostic yield of a closed pleural biopsy, a total of 222 pleural biopsies were performed on 163 patients who had exudative type pleural effusions in a Bronx Veterans hospital from 1962-1969.<sup>4</sup> There was a 28% (46/163) positive yield on the initial biopsy and, more important, there was an additional 28% (14/50) positive yield in performing a second biopsy if the first one was nondiagnostic. There was only an 11% (1/9) added yield in performing a third biopsy if the first two were nondiagnostic. Overall, the pleural biopsy was diagnostic in: 1) 28% of the biopsies, 2) 37% of the patients, 3) 40% of the cancer patients, 4) 71% of the TB patients, and 5) 53% of the cancer or TB patients.

#### RECOMMENDATIONS

Thoracentesis should be performed on any undiagnosed pleural effusion and diagnostic studies should be done on the fluid obtained. If the first thoracentesis does not produce diagnostic information, then the effusion should be tapped a second and sometimes even a third time.

Effusions should be characterized as transudates or exudates by measuring pleural fluid LDH and total protein and by comparing these pleural fluid values with serum LDH and total protein as previously outlined.<sup>3</sup> A transudate indicates that the fluid has accumulated as a result of a systemic disease and that the pleural space is an "innocent bystander." An exudate indicates that the pleural fluid has accumulated as a result of local inflammatory processes within the pleural space. In specific circumstances, the WBC and differential, glucose and amylase measurements of pleural fluid will also be helpful if the fluid is an exudate.<sup>7,8</sup>

Aerobic cultures of every pleural fluid should be performed in spite of its low yield, in view of the efficacy of treatment and the devastating results of failure to recognize aerobic infection in the pleural space.<sup>1</sup> The presence of pneumonia or infection elsewhere in the body, immuno-suppression, sepsis, fever, or positive PPD would be indications to

perform anaerobic, fungal or TB cultures of a pleural fluid.<sup>1,10,11</sup>

Pleural fluid pH, when properly performed and interpreted, is a reliable, rapid method to ascertain the presence of an empyema.<sup>2,5</sup> Cytopathology should also be performed on all pleural fluids as it is the most sensitive way to detect carcinoma in the pleural space.<sup>1</sup> Closed pleural biopsies should be performed on all undiagnosed exudates and repeated once if the first biopsy is unrevealing. If the second closed pleural biopsy is still nondiagnostic, then the patient should undergo an open thoracotomy or fiberoptic pleuroscopy for diagnosis.<sup>4</sup>

#### SUMMARY

A diagnostic thoracentesis should be performed on all pleural effusions. The fluid should be classified as a transudate or exudate by measuring the pleural fluid LDH and total protein, and by comparing these values with serum LDH and total protein values. Cytopathology and aerobic cultures should be done on all fluid. Closed pleural biopsy should be performed on any undiagnosed exudate. The thoracentesis may need to be repeated several times and the pleural biopsy at least twice before a definitive diagnosis can be made. A protocol to systematically evaluate an undiagnosed pleural effusion is included at the end of this paper.

#### ACKNOWLEDGMENT

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## Clinical Use of Anticoagulant Drugs

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Thromboembolic occlusive vascular disease is a major cause of morbidity and mortality in developed countries. This review deals with drugs used to prevent formation of thrombi or to limit their extension.

Anticoagulant drugs interfere with the formation or function of those plasma proteins which interact to form fibrin, a complex protein that is a major constituent of all thrombi. These drugs may be given to prevent the development of thrombi in susceptible individuals, or to prevent their extension and subsequent embolization in situations where thrombi have already formed. The anticoagulants in common use are: heparin, a naturally occurring anticoagulant that must be given parenterally; and the coumarins and indanediones, drugs that can be given orally. Several other agents have been used, but their value remains to be established. These include: defibrinating enzymes extracted from viper venoms (eg, anrod); thrombolytic agents (eg, urokinase, streptokinase); and antiplatelet drugs (eg, aspirin, dipyridamole, dextrans).

### PATHOPHYSIOLOGY OF THROMBUS FORMATION AND DISSOLUTION

Several factors influence the development of thrombi in large vessels — abnormal blood flow, abnormalities in vessel wall, platelet adhesion and aggregation, and blood coagulation.<sup>1</sup> Thrombi consist of a platelet head, that also contains white cells and a small amount of fibrin and entrapped red cells and white cells. The platelet head is large in arterial thrombi and the fibrin tail is large in venous thrombi.

The initiating event in pathological thrombus formation is thought to be platelet adhesion to a damaged area of vessel wall, followed rapidly by aggregation of other platelets that make available a variety of substances, including phospholipids. These substances activate circulating plasma proteins that initiate a biochemical "amplification" system (intrinsic thromboplastin system) (Figure 1). This system is responsible for production of significant quantities of thrombin which then converts circulating fibrinogen to fibrin. Thrombin can also be produced by an alternative pathway that is acti-

vated by damage leading to disruption of the vessel wall (extrinsic thromboplastin system). Preformed fibrin can be converted into soluble constituents (fibrin degradation products) by the action of plasmin, a powerful protease formed by the action of activating enzymes on the circulating protein plasminogen. These plasminogen activators are present in all tissues, and in particularly high concentrations in vascular endothelium.

### HEPARIN

Heparin is a sulfated mucopolysaccharide with a strong electro-negative charge that occurs naturally in tissue mast cells, in liver, and in lung. Commercial preparations are usually obtained from beef lung. Since these preparations vary in potency, their activity is measured in standardized units rather than in milligrams. The sodium salt of heparin is most widely used, and is available in single-dose ampuls or multi-dose vials in strengths of 1,000, 5,000, 10,000, 15,000, 20,000 and 40,000 units/ml. A gelatin depot preparation (20,000 units/ml) is available for subcutaneous injection. Heparin must be given parenterally since it is inactivated by gastric acid. Heparin is eliminated partly by hepatic metabolism and partly by renal excretion in an active form.

When given in doses of 20,000 to 60,000 units per day, heparin has an antithrombin action, thus inhibiting the conversion of fibrinogen to fibrin (Figure 2) and prolonging blood and plasma clotting times. The mechanism of this antithrombin action appears to be the activation of the naturally occurring substance, antithrombin III. In addition, heparin inactivates several other activated coagulation factors (factor IX, factor X, factor XI).<sup>2</sup> Lower doses of heparin (10,000 to 15,000 units per day subcutaneously) inhibit factor X, but have no antithrombin effect and do not prolong clotting times.

Other actions of heparin include an ill-defined effect on platelets, which themselves may release a heparin-neutralizing substance,<sup>3</sup> and an increase in circulating lipoprotein-lipase activity.

Heparin may be administered subcutaneously or intravenously. Intramuscular injections should not be given, since painful hematomas may result. Subcutaneous heparin may be given in low dosage (eg, 5,000 units two or three times daily) for prophylaxis against venous thrombosis in patients at risk (eg, before and after major surgery) or in full dosage (eg, 10,000 units three times daily) for treatment of established thrombosis, when treating outpatients, or

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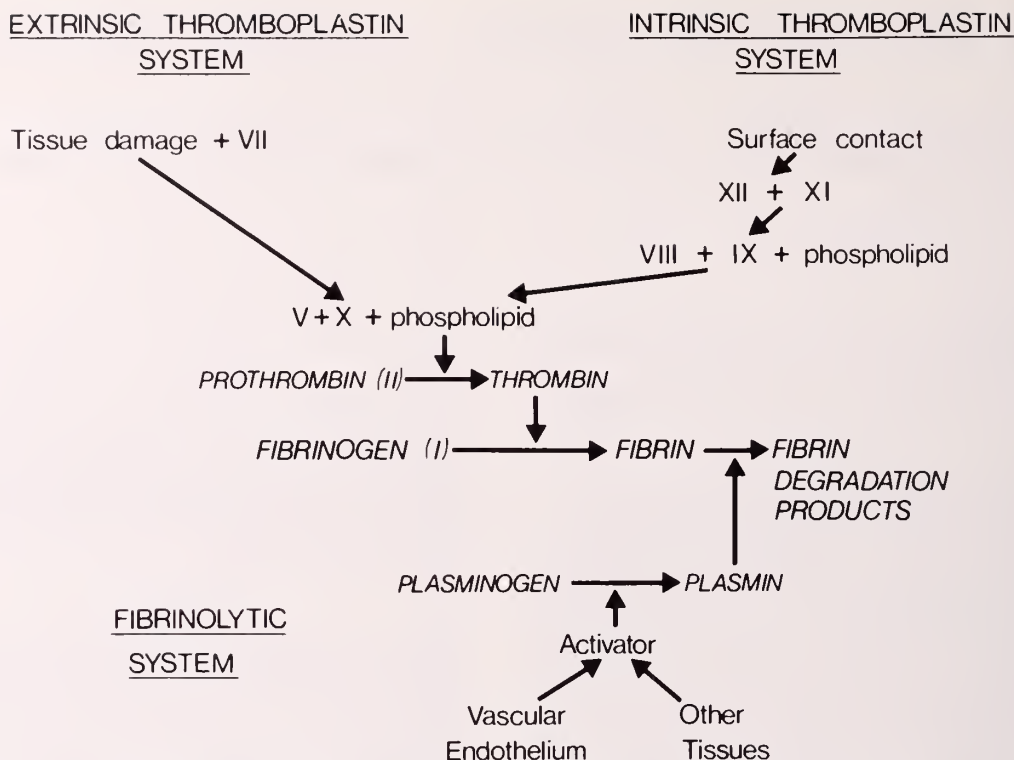


Fig. 1. Coagulation and fibrinolytic systems. Coagulation factors are indicated by Roman numerals.

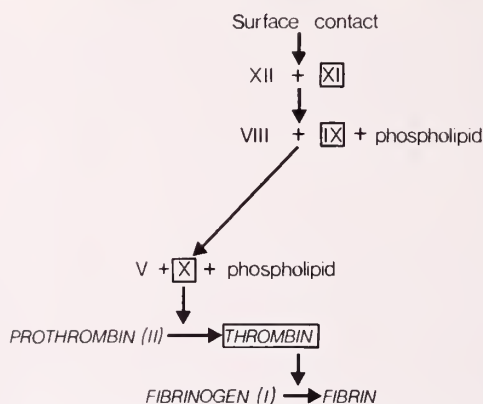


Fig. 2. Sites of action of heparin (indicated by boxes). Low-dose heparin inactivates only factor X.

where access to veins proves difficult. Care in the technique of deep subcutaneous injection is important to avoid local hematoma formation. The intravenous route is the preferred method of heparin administration and should be used when rapid anticoagulation is required. Injections may be intermittent or continuous, with no clear advantage of one or the other. There is a wide variation in the dose required to attain standardized prolongation of clotting times (see below). The usual dose is 5,000 to 10,000 units every 4 to 6 hours for the intermittent injection method, and 1,000 to 2,000 units hourly for the continuous infusion.<sup>4</sup>

#### Laboratory Control

Animal experiments suggest that the whole blood

clotting time should be prolonged to the range of 2 to 3 times normal (ie, 15 to 20 minutes in man) in order to prevent extension of thrombosis. Unfortunately, this test is poorly reproducible, time-consuming, and should be performed at the bedside. The time taken to perform it can be reduced by activation with kaolin and phospholipid (activated whole blood clotting time). Citrated plasma clotting times (partial thromboplastin time, activated partial thromboplastin time, thrombin clotting time) are more reproducible, require less time, and can be performed in batches in the laboratory. However, the tests do not always correlate well with each other. Whichever test is used, the clinician should ensure that, when taking the sample (a) a vein distant from the site of heparin administration is used, (b) traumatic venipuncture, which results in falsely short clotting times, is avoided, (c) when intermittent injections are used, the sample is taken shortly *before* an injection. With continuous infusion, the time of sampling is unimportant. There is a wide individual variation in the dose of heparin required to achieve the desired level of anticoagulation. This appears to be independent of weight and may be due to variation in coagulation factor concentrations<sup>2</sup> and platelet heparin neutralizing activity,<sup>3</sup> as well as variation in the metabolic and renal clearance rates of heparin. Moreover, sensitivity to heparin is not constant at all times; relative resistance commonly occurs after a thrombotic episode.

The desired level of prolongation of the clotting times in patients receiving heparin is not well de-

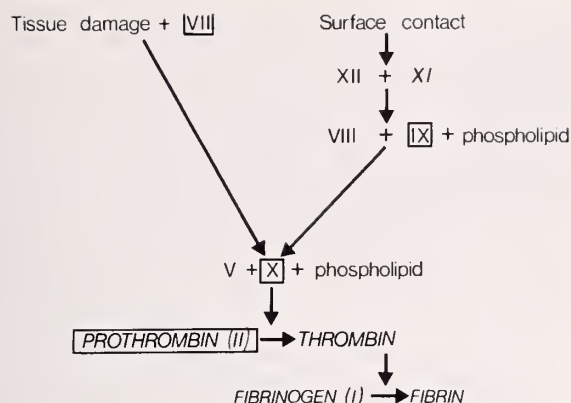


Fig. 3. Sites of action of oral anticoagulants (indicated by boxes).

fin. However, bleeding appears to occur more commonly when tests indicate relative overdosage and recurrent thrombosis is more common when tests indicate relative underdosage.<sup>5</sup> One prospective randomized trial found no difference in the frequency of hemorrhage in those treated with a standard regimen of bolus injections and those whose bolus dosage was altered according to the partial thromboplastin time (PTT). However, a third group given heparin continuously by infusion at doses controlled by the PTT had a significantly lower incidence of major hemorrhage and no higher prevalence of rethrombosis despite receiving less heparin than the other groups.<sup>6</sup> Further studies of the administration and control of heparin therapy are needed.

### ORAL ANTICOAGULANTS

There are two groups of oral anticoagulants — coumarin derivatives (eg, warfarin, dicumarol, acenocoumarol, phenprocoumon) and indanedione derivatives (eg, phenindione, diphenadione, anisindione). The choice of drugs is influenced by two factors — toxicity and duration of action. While the most common adverse reaction to oral anticoagulants is bleeding, the indanedione drugs, particularly phenindione, have also been associated with hypersensitivity reactions (see below), especially in the first few weeks of therapy. Coumarin derivatives are probably preferable for new patients requiring anticoagulant therapy. Drugs with a long duration of action produce a smooth anticoagulant effect when given once daily.

Warfarin, a coumarin derivative with a relatively long duration of action, is now the most widely used oral anticoagulant drug. It is well absorbed when taken by mouth and is available in tablets of various strengths (2 to 25 mg), reflecting the wide individual variation in daily dose requirements. An injectable form for intramuscular or intravenous use is available if oral drugs cannot be given, but its onset of action is not more rapid than orally-administered warfarin.

Oral anticoagulants reduce the hepatic synthesis of the functional forms of the four vitamin

K-dependent coagulation factors — II (prothrombin), VII, IX, and X (Figure 3). Depression of plasma levels of these factors is delayed for at least 12 to 24 hours after the initial administration of oral anticoagulants; 3 to 5 days are usually required to achieve predictable depression of all four factors to the "therapeutic range." The effect of oral anticoagulants may be reversed gradually by vitamin K administration; for immediate reversal, fresh frozen plasma or coagulation factor concentrates are required.

### Laboratory Control

The prothrombin time, prothrombin and proconvertin (P and P) test, and Thrombotest are coagulation tests that are prolonged when vitamin K-dependent factors are reduced and, accordingly, they are used to monitor oral anticoagulant therapy. A tissue extract (thromboplastin) is added to citrated plasma to initiate coagulation via the extrinsic system. There is wide variation between different preparations of thromboplastin in sensitivity to anticoagulants, hence variation in test results between laboratories. This can be avoided by using a standard reagent (eg, Thrombotest) for checking thromboplastins against lyophilized plasma standards. The results of laboratory tests may be expressed as a percentage of normal coagulant activity or as a ratio to the control coagulation time. The "therapeutic range" at which both thrombosis and bleeding should be minimized depends on the type of test and on local laboratory conditions. In general, the prothrombin time should be prolonged to between 2 and 2.5 times the normal (control) time (20 to 30 percent of normal coagulant activity). Coagulant activity ranges for the "P and P" test are 10 to 20 percent and for the Thrombotest, 5 to 15 percent; however, the local laboratory recommendations should be followed. With individual patients, one may aim for either end of the therapeutic range, depending on whether the risk of thrombosis or of bleeding is thought greater. Since heparin also prolongs these clotting times, samples should be taken not sooner than five hours after an intravenous bolus injection of heparin; controlled infusion of heparin does not significantly affect the prothrombin time.<sup>6</sup>

Warfarin is well absorbed orally, is 97 percent protein-bound, and has a relatively small volume of distribution. Thus, even small changes in the degree of protein-binding may lead to large changes in the amount of circulating free (active) warfarin, and hence in the anticoagulant activity observed in the patient. Since warfarin is an asymmetric molecule, the commercially available preparations contain two stereoisomers — D- and L-warfarin. These isomers are eliminated at different rates, have different anticoagulant activities, and respond differently to the presence of other drugs.<sup>7</sup> Thus, it is not surprising that the range of dosage of warfarin re-

TABLE 1

DRUGS AFFECTING THE RESPONSE TO ORAL ANTICOAGULANTS<sup>a</sup>

(A) <i>Drugs increasing the activity of anticoagulants</i>	
Broad spectrum antibiotics	Proposed Mechanism
Mineral oil, cholestyramine	Reduced bacterial synthesis of vitamin K
Salicylates, mefenamic acid,	Reduced absorption of vitamin K
indomethacin, phenylbutazone,	Increased activity of anticoagulant due
clofibrate, chloral hydrate,	to displacement from plasma albumin
sulfonamides, nalidixic acid,	
diazoxide, ethacrynic acid,	
tolbutamide, probenecid,	
phenytoin	
Disulfiram, clofibrate, chlor-	Reduced metabolism of anticoagulant due
promazine, reserpine, tricyclic	to inhibition of liver microsomal
antidepressants, chloramphenicol,	enzymes
colchicine, allopurinol,	
metronidazole	
Salicylates, clofibrate, glucagon,	Increased anticoagulant action due to
thyroxine, quinine, quinidine,	other mechanisms
chloroquine, anabolic steroids	
(B) <i>Drugs reducing the activity of anticoagulants</i>	
Vitamin K	Proposed Mechanism
Barbiturates, dichloralphenazone,	Competitive inhibition
glutethimide, ethchlorvynol,	Increased metabolism of anticoagulant due
griseofulvin, rifampin,	to induction of liver microsomal
spironolactone	enzymes

<sup>a</sup>See also reviews by Deykin,<sup>8</sup> Sigell and Flessa,<sup>9</sup> and Koch-Weser and Sellers<sup>10</sup>

quired to maintain a given level of anticoagulation varies widely from patient to patient and may be altered by several factors.

#### *Factors Influencing the Response to Oral Anticoagulants*

Several patient factors, as well as many commonly used drugs, alter the response to oral anticoagulants. Smaller doses are usually required in females, the elderly, individuals of small body size, the acutely ill, patients with hepatobiliary disease, and patients with renal impairment. Larger doses may be required in myxedema, and in patients eating diets rich in vitamin K (fruit and green vegetables). Bleeding may occur if a drug is given that increases the activity of the anticoagulant, or if a drug that reduces activity of the anticoagulant (eg, a barbiturate) is suddenly stopped without reducing the dose of the anticoagulant. Some drugs that alter the effects of oral anticoagulants are listed in Table 1; it should be noted that the mechanisms of interaction are not always well defined and that the clinical significance of most of the interactions is uncertain. However, concurrent use of any of these drugs with oral anticoagulants merits frequent laboratory control. Anti-inflammatory drugs (salicylates, indomethacin, phenylbutazone) not only may potentiate the effect of anticoagulants but also have antiplatelet and ulcerogenic actions; for these reasons they should be avoided in anticoagulated patients. For further information the reader is referred to the detailed reviews of this topic by Deykin,<sup>8</sup> Sigell and Flessa,<sup>9</sup> and Koch-Weser and Sellers.<sup>10</sup>

#### *Dosage and Administration*

Traditionally a large loading dose of warfarin (20 to 60 mg) is given over the first 24 to 48 hours; however, a small initial dose (10 to 15 mg daily) is simpler and may reduce the risk of bleeding during induction in sensitive patients.<sup>8,11</sup> Whatever initial dose scheme is adopted, the daily maintenance dose after 48 hours treatment should be determined by laboratory tests; tests should be performed daily at first, reducing the frequency of testing as stabilization ensues. The daily maintenance dose of warfarin usually lies between 2 and 25 mg. True warfarin resistance is rare, relative (ie, overcome by increasing the dose of warfarin), and inherited as an autosomal dominant characteristic.<sup>12</sup> Before diagnosing resistance, it should be ensured that the patient is taking and absorbing the tablets and that antagonistic drugs are not being administered.

For characteristics and dosage of other oral anticoagulant drugs, the reader is referred to the appropriate literature.

#### *Outpatient Anticoagulation*

Before discharge from the hospital, patients should be educated in the nature of anticoagulant therapy, the variability of effect, and the necessity for regular attendance at the anticoagulant clinic for control of therapy. He should be warned not to make radical dietary changes and to avoid excessive alcohol intake, any use of aspirin or other preparations containing salicylates, and other self-medication. Acetaminophen (paracetamol) may be recommended as an alternative simple analgesic.

The patients should be told to seek medical attention in the event of bleeding (eg, melena, hematuria) or acute illness and to carry at all times a dosage and test result card and to show it to his medical and dental practitioners; the patient's blood group should also be recorded on this card. This advice should be reinforced by a simple booklet and by nurses and pharmacists. The patient's primary care physician and dentist should be made aware of the hazards of prescribing or withdrawing other drugs without frequent laboratory monitoring of anticoagulant effect.

### *Cessation of Anticoagulant Therapy*

Recent trials suggest that there is no increased incidence of arterial or venous thromboembolism when anticoagulants are stopped abruptly, rather than tapered over a few weeks.<sup>13-15</sup>

### INDICATIONS FOR ANTICOAGULANTS

Although anticoagulants are used widely in the management of thrombosis, few well conducted trials have been done to provide objective support for their use. The introduction of both heparin and the oral anticoagulants preceded the general acceptance of the need for critical assessment of drugs by prospective, controlled, randomized, double-blind trials. Even now, therapeutic trials in thrombotic diseases present several major problems. Difficulties arise in defining the endpoint of a trial; assessment of mortality rate is complicated by "non-thrombotic" deaths, especially in older patients with multiple disease processes. On the other hand, a nonfatal thrombotic recurrence or an extension of an existing thrombus may be extremely difficult to detect. The desirable level of anticoagulation and the duration of treatment are not universally agreed upon. Large numbers of patients may be required to obtain a convincing result if the benefit of treatment is small; multicenter trials are then required but present major problems in organization. Finally, many clinicians would maintain that the currently available evidence of benefit from anticoagulation in, for example, acute pulmonary embolism is sufficient to render unethical the inclusion of a non-anticoagulated control group in any trial.<sup>16</sup> For these reasons most indications for anticoagulant therapy (Table 2) are imperfectly established.

### *Prevention of Venous Thromboembolism in Patients at Risk*

In certain patients at high risk of deep vein thrombosis and pulmonary embolism (eg, patients who have had major surgery), preventive anticoagulation during periods of immobility may be justified. Since the clinical diagnosis of venous thrombosis is notoriously unreliable anticoagulation is particularly justifiable; over fifty percent of patients with active thrombus formation detected by <sup>125</sup>I-fibrinogen scans have no clinical signs.<sup>17</sup> Moreover,

TABLE 2

#### INDICATIONS FOR ANTICOAGULANT THERAPY

Prevention of venous thromboembolism in patients at high risk
Established pulmonary embolism and/or deep vein thrombosis
Rheumatic mitral valve disease
Prosthetic heart valves
After coronary artery surgery
Myocardial infarction — short-term and/or long-term
Transient cerebral ischemic attacks
Acute peripheral arterial occlusion
Special uses of heparin in hospital:
Maintenance of patent infusion sites
Hemodialysis, arterial surgery, cardiac bypass surgery
Disseminated intravascular coagulation

TABLE 3

#### SELECTED RISK FACTORS FOR POST OPERATIVE THROMBOSIS

Age over 40 years
Immobility
Cardiac failure
Obesity
Varicose veins
Previous pulmonary embolism or deep vein thrombosis
Malignant disease
Operations on hip, pelvis, lower limb
Trauma

many patients die from pulmonary embolism arising from clinically "silent" venous thrombosis before treatment can be instituted. At present, routine screening for early thrombosis with active treatment of those with positive tests appears less practicable than widespread prophylactic anticoagulation.

In controlled trials, oral anticoagulants reduce clinical and autopsy thromboembolism (by about 75 percent on average) in patients with hip fractures,<sup>18,19</sup> undergoing elective hip surgery,<sup>20</sup> undergoing major general surgery,<sup>21</sup> and with congestive cardiac failure.<sup>22</sup> A consistent trend towards reduction in mortality was observed in these studies, specifically due to reduction in fatal pulmonary embolism. On the other hand, the incidence of major hemorrhage in treated patients appeared to be increased two-fold over control subjects. This fact, together with the need for employing regular control tests with individual patient dosage, has probably limited the widespread use of prophylactic oral anticoagulants.

In recent years, low doses of subcutaneous heparin have been used as an alternative method of peri-operative anticoagulation; no control tests are required, a standard dose is used, and the risk of hemorrhage appears less than with oral anticoagulants. In a recent large multicenter trial, low doses of heparin, given to patients aged over 40 undergoing elective general surgery, reduced the incidence of pulmonary embolism detected at autopsy, as well as reducing the incidence of venous thrombosis (clinical, isotopically-detected, and seen at post-mortem).<sup>23</sup> The demonstration of a reduction in total mortality would, however, require a much larger trial. A slight increase in the number of wound

hematomas was seen. The efficacy of low-dose heparin in hip surgery has not been proven,<sup>24,25</sup> and at present oral anticoagulants should be used in this situation. As an alternative to anticoagulants, intravenous dextran-70 has also been shown to prevent pulmonary embolism after major general surgery.<sup>26</sup>

In assessing individual patients for anticoagulant prophylaxis prior to major surgery, thrombotic risk factors should be considered (see Table 3).

#### *Treatment of Established Venous Thromboembolism*

**Acute pulmonary embolism.** There is reasonably good evidence that prompt anticoagulation of patients with acute pulmonary embolism reduces the risk of recurrent embolism and lowers mortality from 18 to 32 percent to the range of 1 to 9 percent.<sup>16</sup> Accordingly, intravenous heparin should be started as soon as a provisional clinical diagnosis is made, unless strong contraindications exist. It has been suggested that large intravenous doses be used initially, for two reasons — first, such patients are relatively resistant to heparin;<sup>5</sup> second, large doses of heparin may prevent platelet release of bronchoconstrictor amines.<sup>27</sup> Clinical diagnosis of pulmonary embolism is often difficult, especially in the presence of pre-existing cardiopulmonary disease; the diagnosis should preferably be supported by isotope lung scanning or pulmonary angiography. However, heparin should be started pending the organization of these investigations. If the embolus is massive and the patient's circulation is severely affected, embolectomy or thrombolytic therapy should be considered. When emboli recur despite adequate anticoagulation, ligation or plication of the inferior vena cava may be considered.<sup>28</sup>

**Acute deep vein thrombosis.** There are no controlled trials of anticoagulants in established deep vein thrombosis. However, there is indirect evidence that they prevent extension and embolization of the thrombus. First, prophylactic anticoagulants in at-risk patients reduce the incidence and extent of deep vein thrombosis and pulmonary embolism.<sup>18,19</sup> Second, untreated deep vein thrombosis is associated with pulmonary embolism, especially when proximal to the calf,<sup>29</sup> whereas in anticoagulant-treated deep vein thrombosis pulmonary embolism is rare; when it does occur it is associated with poor anticoagulant response.<sup>30,31</sup> As with pulmonary embolism, clinical diagnosis is unreliable; almost half of patients with clinical "venous thrombosis" have no thrombus evident on venography.<sup>32</sup> Bilateral venography should therefore be performed, if possible, to prevent needless anticoagulation; again, this need not delay the initial use of anticoagulants if clinical suspicion is strong. Venography may reveal the extent and the degree of attachment of the thrombus, as well as confirm the diagnosis.

Iliofemoral thrombosis carries a high risk of major pulmonary embolism in the acute stage, especially if the thrombus is loosely attached to the vein wall. The "post-phlebitic" syndrome of chronic venous insufficiency of the leg secondary to venous valve damage is also a high risk condition. In these situations, thromboectomy or thrombolytic therapy should be considered, although the overall clinical advantage of these procedures over conventional anticoagulants has yet to be demonstrated.<sup>28</sup> If thrombosis is confined to the calf veins, the risks are much smaller, although small pulmonary emboli and extension to the iliofemoral veins may occur. The relative risks of extension and anticoagulation must then be balanced.

Some believe that the achievement of a prothrombin time within the therapeutic range in patients on oral anticoagulants (usually achieved within 24 to 48 hours of starting warfarin) may precede an effective antithrombotic therapeutic effect, which takes 7 to 10 days. Accordingly, they recommend that heparin be continued for several days after oral anticoagulant therapy has been commenced.<sup>8</sup> A possible explanation is that the level of factor VII is disproportionately reduced during the first week of oral anticoagulant therapy, after which all vitamin K-dependent factors are reduced to the same extent;<sup>10</sup> factor VII may be less relevant to thrombosis than the other factors. However, no proper trials exist to determine the relative benefits of short-duration heparin (2 to 4 days) and long-duration heparin (7 to 14 days) in acute venous thromboembolism.

It seems logical to treat immobile patients at least until they can ambulate, and to continue treatment indefinitely in the minority of patients who suffer recurrent documented thromboembolism when anticoagulants are stopped. Although there is some evidence that long-term anticoagulants (ie, 6 months to a year) enhance venous recanalization,<sup>33</sup> the relation of treatment duration to the development of the clinical post-phlebitic syndrome, which may take years to appear, is unknown. With regard to recurrent thromboembolism, a prospective controlled trial has demonstrated that six months treatment is no more effective than six weeks treatment, unless there is a previous history of venous thromboembolism or a continuing predisposing cause.<sup>13</sup>

**Chronic thromboembolic pulmonary hypertension.** Although anticoagulants are usually given on a long term basis to patients with chronic pulmonary hypertension due to recurrent pulmonary embolism, evidence of their benefit is lacking.

#### *Heart Valve Disease*

**Rheumatic mitral valve disease.** There is some evidence that long-term oral anticoagulants, given to patients with chronic rheumatic mitral valve disease, reduce the incidence of pulmonary embolism (from leg veins or the right atrium) and systemic

arterial embolism (from the large, fibrillating left atrium). No proper controlled trials exist; however, many clinicians accept significant mitral valve diseases with a large left atrium as an indication for anticoagulants. It can be argued that one should not wait for the first embolus to occur before starting treatment.

*Prosthetic heart valves.* Similarly, despite the lack of controlled trial data, anticoagulants are often given on a long-term basis to patients with prosthetic heart valves to reduce thromboembolism. More modern valves appear less likely to cause emboli, and the use of anticoagulants appears to be waning.

### *Coronary Artery Disease*

*Myocardial infarction – short-term therapy.* Studies in the 1950's suggested that short-term anticoagulant therapy in acute myocardial infarction halved the mortality rate. In the 1960's, defects in the design of these studies were emphasized, and their conclusions were questioned. Further trials of better design were performed subsequently. Overall, no significant reduction in mortality has been demonstrated; however, some trials have demonstrated a significant reduction in thromboembolic events.<sup>34,35</sup> There may be an increased risk of hemopericardium, possibly complicating pericarditis.<sup>34</sup> Recently, low-dose subcutaneous heparin has been shown to markedly reduce the incidence of deep vein thrombosis detected by <sup>125</sup>I-fibrinogen leg scanning;<sup>25,36</sup> however, the effect of such treatment on clinically significant thromboembolism would require much larger studies. In recent years, other aspects of the treatment of myocardial infarction have changed. The introduction of coronary ambulances and coronary care units may reduce the mortality from acute dysrhythmias and heart block, while early mobilization may reduce the incidence of venous thromboembolism; however, no difference in <sup>125</sup>I-fibrinogen-scan thrombosis was found in one trial of rapid mobilization.<sup>37</sup>

*Myocardial infarction – long-term therapy.* An International Review Group, studying several trials of reasonable design performed in the 1960's, concluded in 1970 that long-term anticoagulant therapy (1 to 2 years) probably results in a slight reduction in mortality in males aged under 55, with either previous angina or a previous infarction.<sup>38</sup> This possible benefit to a minority of the treated patients must be weighed against the cost and effort of long-term anticoagulation of large numbers of patients, the risks of hemorrhage, and, possibly, interference with rehabilitation, invalidism, and "clinic addiction."

*Coronary artery surgery.* Oral anticoagulants are commonly given for some weeks or months after bypass grafting of the coronary arteries to prevent graft thrombosis. Controlled trials are lacking.

*Angina pectoris.* In the rather ill-defined syndrome of "acute coronary insufficiency" or "un-

stable angina," as well as in chronic stable angina, there is a lack of adequate controlled trial data to determine whether anticoagulant therapy is of benefit. In recent years, the emphasis in treatment of these conditions has swung to the use of beta-adrenergic blocking drugs and coronary artery surgery.

### *Peripheral Arterial Disease*

There is no evidence that chronic anticoagulant therapy is of benefit in peripheral arterial disease. Although heparin is often given to patients with acute arterial occlusion, benefit is uncertain here, also.

### *Cerebral Arterial Disease*

*Transient ischemic attacks.* Most trials of reasonable design suggest that oral anticoagulants reduce the incidence of transient cerebral ischemic attacks, at least for the first year of treatment. The effect after this time and on mortality are unproven.

*Evolving strokes and completed strokes.* There is no definite proof that anticoagulants are of value either in the acute phase of stroke or when given long-term after a completed stroke. Furthermore, there may be an increased mortality from cerebral hemorrhage or because there is bleeding into a softened infarct or from diseased cerebral vessels. Cerebral embolism after mitral valve disease tends to recur, and anticoagulants are then commonly given; however, since hemorrhage may occur into the softened infarct many clinicians wait for a few days before commencing oral anticoagulants — this risk period is not well defined.

### *Renal Disease*

It has been suggested that anticoagulants may prevent glomerular fibrin deposition in progressive glomerular disease, but no controlled studies have been reported.

### *Special Uses of Heparin in Hospital*

Heparin is used in low doses to maintain the patency of infusion sites. Normal doses are given in arterial surgery to prevent thrombosis and blood clotting outside the body in cardiac bypass surgery and hemodialysis.

Disseminated intravascular coagulation may complicate a wide variety of acute illnesses and operations. A more chronic form is seen in malignant disease, retained dead fetus, and giant hemangioma. The coagulation process is activated by release of thromboplastins from damaged tissues or by widespread damage to the endothelial lining of small blood vessels. Clinical features include thrombosis, anemia, from damage to red cells by fibrin strands in the capillaries, and bleeding due to depletion of fibrinogen, platelets and other coagulation factors, as well as release of anticoagulant fibrin degradation products. Management includes treatment of the

TABLE 4

## CONTRAINDICATIONS TO ANTICOAGULANT THERAPY

<i>Hemostatic defect</i>
Congenital clotting factor defects (eg, hemophilia)
Acquired clotting factor defects (eg, liver disease, obstructive jaundice, steatorrhea)
Thrombocytopenia
<i>Hemorrhagic lesions</i>
Active bleeding
Active peptic ulcer, esophagitis, colitis, or diverticulitis
Esophageal varices
Gastrointestinal or urinary tract malignancy
Recent liver or renal biopsy
Threatened abortion
Recent surgery trauma to brain, eye, or spinal cord
Recent lumbar block anesthesia
Recent cerebrovascular accident
Severe hypertension
Arterial aneurysm
Vascular retinopathy (risk of retinal or vitreous hemorrhage)
Infective endocarditis (risk of cerebral hemorrhage from aneurysms)
Acute pericarditis
<i>Use of drugs with anti-platelet/ulcerogenic activity</i>
Salicylates, indomethacin, phenylbutazone, oxyphenbutazone
<i>Additional contraindications to long-term therapy</i>
Unreliability (eg, alcoholism, psychopaths, unsupervised mental defectives)
Inadequate facilities for drug control and treatment of bleeding
Need for intensive salicylate therapy

underlying disease process, treatment of shock with blood transfusion and oxygen, and replacement of clotting factors and platelets to correct the bleeding tendency. Heparin treatment is controversial; it may correct coagulation test abnormalities but does not appear to reduce overall mortality in acute disseminated intravascular coagulation.<sup>39</sup> Some authors advocate the use of heparin in more chronic situations, to restore hemostasis pending removal of a dead fetus or giant hemangioma, or to allow diagnosis or treatment of malignancy. As heparin may aggravate the bleeding, if given it should be used with great caution and under careful laboratory control.

## CONTRAINDICATIONS TO ANTICOAGULANTS

Anticoagulants are contraindicated when the risk of adverse effects (usually hemorrhage) outweighs the potential benefit of anticoagulation (Table 4). Patients may be susceptible to hemorrhage because of a general hemostatic defect, because of an actual or potential bleeding lesion, or because of concurrent therapy with antiplatelet or ulcerogenic drugs. Many of the contraindications listed in Table 4 are relative rather than absolute; the risks must be balanced against the need for treatment.

## SPECIAL PRECAUTIONS (Table 5)

*Pregnancy and Puerperium*

Oral anticoagulants cross the placental barrier, are potentially teratogenic in the first trimester of pregnancy, and can cause fetal and placental hemorrhage, especially under the physical stress of vaginal delivery.<sup>40</sup> Heparin does not cross the placental barrier; some authors advocate the sole use of heparin as an anticoagulant when this is indicated during

TABLE 5

## SPECIAL PRECAUTIONS IN ANTICOAGULANT THERAPY

Pregnancy and puerperium
Surgery and dental extraction
Congestive cardiac failure
Females aged over 60 years

pregnancy (using subcutaneous injections, possibly self-administered, as an outpatient) but the practical problems are obvious. A reasonable compromise would be to use heparin for the remainder of the first trimester after diagnosis of pregnancy, and to use oral anticoagulants thereafter under strict laboratory control. At 37 weeks the patient is admitted to hospital and oral anticoagulants replaced by heparin, which is stopped when labor commences. Some hours after delivery heparin and oral anticoagulants may be restarted; breast-feeding should be avoided in patients taking oral anticoagulants as these drugs are excreted in milk.

*Surgery*

When patients on oral anticoagulants undergo surgery (including dental extraction) they should be admitted to hospital and the dose reduced or stopped to allow return of coagulation tests to levels of moderate anticoagulation, or to normal levels where the risk of bleeding is great (eg, eye or neurosurgery) for the immediate perioperative period. When the need for emergency surgery arises, vitamin K<sub>1</sub> or coagulation factor replacement may be required to reverse the bleeding tendency, preferably with laboratory control (see section on treatment of hemorrhage). Careful laboratory control of anticoagulants is required in the postoperative period, especially in the presence of indwelling drains or catheters since

they are associated with increased risks of bleeding.

### *Congestive Cardiac Failure*

As well as being prone to thrombosis, patients in cardiac failure are more likely to bleed when on anticoagulants than normal subjects, possibly due to liver dysfunction.

### *Elderly Females*

Anticoagulants should be used with caution in female patients over age 60 that have a high risk of hemorrhage.<sup>41</sup>

## **HEMORRHAGE DURING ANTICOAGULATION**

Bleeding is an ever-present hazard of anticoagulant therapy. In Britain, in 1967, anticoagulants were the second most common reported cause of drug-related death (after corticosteroids); death was usually from gastrointestinal or cerebral hemorrhage.<sup>42</sup> Bleeding is sometimes due to overdosage (as determined by clotting times prolonged beyond the therapeutic range), but it can also occur in patients with therapeutic or subtherapeutic clotting times; in the latter case, hemorrhage is usually due to a defective hemostatic system or vascular tree or a bleeding lesion. Serious hemorrhage occurs frequently from an unsuspected, clinically silent peptic ulcer, cerebral aneurysm, or neoplasm. The increased risk of bleeding in elderly females, patients with heart failure, and patients with indwelling devices and recent surgical wounds, has already been mentioned.

Minor hemorrhage may require no action, other than temporary cessation of therapy or reduction in dosage, if tests indicate overdosage. Major hemorrhage may require withdrawal of anticoagulants, blood transfusions to maintain blood volume and tissue perfusion and to correct anemia, reversal of anticoagulant effect (see below), and, in special situations, consideration of surgical procedures once the coagulation defect is corrected (eg, nasal packing, pericardial aspiration, undersewing of peptic ulcer, removal of an intracranial or intraspinal hematoma).

### *Reversal of Heparin Effect*

Since heparin has a short plasma half-life, cessation of intravenous therapy usually renders the patient hemostatic within a few hours. In urgent situations, protamine sulfate may be injected intravenously. Protamine, which is strongly basic, instantly neutralizes heparin, which is strongly acidic; its effect lasts about two hours. The concentration of the commercially available solution is 10 mg/ml; 1 mg of protamine neutralizes about 100 units of circulating heparin. A dose of 50 mg, injected slowly intravenously over 10 minutes, is usually adequate but can be repeated up to a total dose of 200 mg in two hours. The exact dose required may be determined in the laboratory by titration (eg, in cardiac bypass surgery). In the absence of heparin or in

excess, protamine itself is an anticoagulant. Other potential adverse effects are due to depression of cardiac muscle and vascular smooth muscle, and include dyspnea, bradycardia, tachycardia, hypotension, and flushing.

### *Reversal of Oral Anticoagulants*

On cessation of warfarin therapy the patient may remain anticoagulated for 48 hours or more. Vitamin K<sub>1</sub> (phytonadione) may be given orally or intravenously to speed the return of adequate concentrations of vitamin K-dependent clotting factors; the response to intravenous therapy is no more rapid than the response to vitamin K given orally. There is marked individual variation in the response to vitamin K: some patients may be rendered hemostatic in 6 hours while others may not be until 24 hours.<sup>43</sup> A dose of 5 to 15 mg may be given in less urgent situations and will allow continuing anticoagulant therapy; doses of 20 to 50 mg may be given if hemorrhage is severe, but will render the patient refractory to further oral anticoagulant therapy for up to 2 weeks. In urgent situations, the depleted levels of factors II, VII, IX and X can be rapidly restored by infusion of plasma or whole blood; stored plasma is adequate as all four factors are relatively stable on storage. Usually one unit (500 ml) of plasma is sufficient to control bleeding. Stable factor IX concentrates, which contain all of these coagulation factors, are available; however, they carry a greater risk of hepatitis, and in addition the risk of thromboembolism due to activated coagulation factors, especially in patients with liver disease. Factor replacement is preferably monitored by coagulation tests.

## **OTHER ADVERSE EFFECTS OF ANTICOAGULANTS**

Adverse reactions other than hemorrhage are uncommon. Some of these are described below.

### *Heparin*

Acute hypersensitivity reactions may be generalized and sometimes fatal: a trial dose of 1000 units may be advisable in patients with a history of other allergies. Local reactions may follow subcutaneous injections of heparin. Acute thrombocytopenia may occur after a week and is probably also a hypersensitive reaction. Burning feet and priapism as well as acute arterial thrombosis have also been described during treatment. Prolonged heparin therapy has been associated with transient alopecia, osteoporosis, and in children overgrowth of eyelashes and eyebrows.

### *Oral Anticoagulants*

Skin necrosis, due to a vasculitis, may occur 3 to 10 days after the start of therapy; blistering is followed by necrosis and sloughing, and usually occurs on the breasts, trunk and thighs. Purple toes, with pain and discoloration but not necrosis, and tran-

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sient alopecia have been recorded. Red or orange coloration of the urine from indanedione drugs may cause confusion with hematuria. Much more serious results of indanedione therapy are various hypersensitivity reactions; they are most common with phenindione and usually occur in the first six weeks of therapy. Fever, diarrhea, hepatitis, thrombocytopenia, leucopenia and agranulocytosis, renal tubular necrosis, and exfoliative dermatitis have been described. Coumarin anticoagulants are usually tolerated by indanedione-sensitive patients. Finally, patients have been described who become addicted to long-term anticoagulant clinics and suffer withdrawal symptoms when attendance is stopped; surreptitious ingestion of oral anticoagulants to cause hemorrhage has also been seen as a variant of Munchhausen's syndrome.<sup>44</sup>

#### CONCLUSION

Anticoagulants were claimed to be universally effective antithrombotic agents in the 1950's. In more recent years, doubts have been raised in virtually every situation in which their use was advocated. Widespread use, based on early testimonials, contrasts with the paucity of reliable data from proper controlled clinical trials. Indeed, in a recent review, McNicol states that "If heparin were a new medication, it is highly unlikely that the evidence in its favour would be acceptable and I can imagine the cynicism if not the scorn with which a submission to the Food and Drug Administration would be greeted if a manufacturer were to ask for permission to market heparin on today's evidence for the treatment of established thromboembolic disease."<sup>45</sup> In another review, Mitchell observed that "Nearly three decades ago Solandt, Nassim and Best studied the effect of anticoagulants on experimental cardiac infarction and two decades have elapsed since the first application of these agents to the management of human disease, yet there is still little general agreement about their value. Thirty years of confusion is an appalling indictment of our methods of appraising the action of new therapeutic agents."<sup>46</sup>

Nonetheless, today's evidence must guide today's therapy, imperfect as both the evidence and the therapy are. At present anticoagulants appear to have a place in the prevention and treatment of venous thromboembolism, in the prevention of embolism from abnormal heart valves, and to stop blood clotting when it passes through machines. Accurate diagnosis of venous thromboembolism, careful patient selection, awareness of drug interactions, and regular laboratory control may reduce the number of bleeding complications and hence increase the safety of anticoagulant therapy.

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# *From the Secretary's Notebook*

## Summary of 1977 Annual Meeting of the M.M.A. House of Delegates

June 11 and 12, 1977 at Rockport, Maine

The 124th annual session of the M.M.A. House of Delegates was held at the Treadway-Samoset Resort in Rockport, Maine with a registered attendance of seventy-one delegates, fourteen alternates and twenty-four guests. The first session was convened on Saturday, June 11, at 2:00 P.M., and the second session on Sunday, June 12, at 2:00 P.M. Richard C. Leck, M.D., President of the M.M.A., called to order the meetings of the House, which were presided over by George W. Bostwick, M.D., Speaker of the House.

**Election of Speaker and Vice Speaker of the House of Delegates for 1977-1978** — George W. Bostwick, M.D. was re-elected Speaker, and A. Dewey Richards, M.D. was elected Vice Speaker.

**Budget for 1978** — The Reference Committee recommended three changes from the Budget as printed: Salary for the Assistant Executive Director to be \$20,000 with \$5,000 in fringe benefits for a total amount of \$25,000, add \$10,000 for the Ad Hoc Committee on Malpractice, and change the total expenditures to \$236,890. The budget, as amended, was subsequently *approved*.

**Committee on Nominations** — A slate was prepared in March at the Interim Meeting of the House of Delegates and presented at this meeting for vote. Due to the untimely death of Dr. Donald L. Anderson, a President as well as a President-elect had to be nominated. Drs. Douglas R. Hill and Martyn A. Vickers, Jr. were nominated for President, and Dr. Francis I. Kittredge was nominated for President-elect. The following officers were elected:

### *President*

Douglas R. Hill, M.D.

### *President-elect*

Francis I. Kittredge, M.D.

### *Executive Committee*

3rd District — John W. Wickenden, M.D.

7th District — Ross W. Green, M.D.

8th District — Charles H. Lightbody, M.D.

### *AMA Delegate*

Robert E. McAfee, M.D.

### *AMA Alternate*

Brinton T. Darlington, M.D.

Dr. William H. Maxwell of Portland was nominated and elected to complete Dr. Hill's term on the Executive Committee for the **2nd District**. The House of Delegates *approved* an expression of gratitude in recognition of the late Dr. Donald Anderson's many years of service to the M.M.A.

The **Standing Committees**, constituted per recommendation of the Committee on Nominations, were *approved*.

*Reports (not included in the House of Delegates' folders) —*

**Executive Director** — Dr. Hanley introduced Mr. D. Jeffrey Hollingsworth, recently hired Assistant Executive Director. A former Belfast resident, Mr. Hollingsworth had previously been employed by the Medical Liability Commission and later as a staff specialist on professional liability with the American Hospital Association, both in Chicago. Dr. Hanley spoke to the delegates on various subjects, among them malpractice, national health insurance, hospital costs, the *Journal* of the M.M.A., and the Maine Medical Education Foundation. Dr. Hanley's report was *accepted*; he was *commended* for his years of service to the M.M.A. and he was given a standing ovation following his stated intention that this would be his final report as Executive Director.

**Committee on Recruitment, Aid & Placement** — Dr. Robert E. McAfee, Chairman, reported that approximately \$60,000 was loaned last year to about 55 students from Maine attending medical schools.

**Committee on Legislation** — Dr. Brinton T. Darlington, Chairman, said that Mr. Cragin, our lobbyist, would give a report on legislative matters, and thanked those physicians who had personally contacted legislators during the year.

**Printed reports** not requiring action (resolutions from committees appear elsewhere in this summary) and *accepted* for information were as follows: Committees — Allied Health Professions, Continuing Education, Care of the Disadvantaged, Emergency Medical Service, Health Care Financ-

ing, Peer Review, Ethics and Discipline, Amy W. Pinkham Fund, Burn Advisory, Conservation of Vision, Diabetes, AMA-ERF, Liaison between the M.M.A. and the Maine Bar Assn., Maternal & Child Welfare, Advisory to the Secretary of State and to the Bureau of Motor Vehicles, and Medical Care in Maine's Prisons; Reports of Secretary-Treasurer, President of the Auxiliary, Executive Committee members and Delegates to Out-of-State Medical Society Meetings.

#### RESOLUTIONS

**Medical Education** — Presented by the Kennebec County Medical Society, this resolution *approved* as amended:

WHEREAS, the House of Delegates of the Maine Medical Association approved in 1972 a resolution to support an innovative approach to medical education as embodied in what came to be known as the "Medical School without walls for Maine," and

WHEREAS, that development failed with the veto of the necessary enabling legislation by the Governor of Maine in 1975 — a veto based on financial considerations, and

WHEREAS, the Governor in his veto message continued to support the objectives of that specific medical education program, and appointed a Committee to study alternative approaches to meeting those objectives, and

WHEREAS, the Committee has rendered a report which has made seven (7) specific recommendations, the principal one being that the Governor "should create a mechanism to perform the specific functions detailed below" — for functions described being those of coordination of the many existing efforts in medical education and recruitment in Maine, and

WHEREAS, the Governor has recommended that Medical Care Development, Inc. be directed to work towards the development of an atmosphere of cooperation and coordination in all medical education efforts in the State including undergraduate, post-graduate, and continuing medical education of physicians as well as the education of para-professional groups, now therefore

BE IT RESOLVED, that the House of Delegates of the Maine Medical Association supports the recommendation of the Governor that Medical Care Development, Inc. assume the leadership and coordination role for further development of Medical Manpower and Education Programs in Maine, and

BE IT FURTHER RESOLVED, that the House of Delegates directs the Maine Medical Association's Executive Director and the appropriate committees of the Association to offer whatever assistance is necessary to Medical Care Development, Inc. and the University of Maine in any current program of Medical Manpower, Re-

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cruitment and Education including the Maine Medical Education Foundation, the Compacts for financing medical school training of students from the State of Maine at the University of Vermont College of Medicine and Tufts University School of Medicine, and the Continuing Medical Education Committee Program including the accreditation of Continuing Medical Education in the State of Maine.

**President's Term on the Executive Committee** — Presented by the Executive Committee, this resolution, which will require a change in the Constitution, was *approved*:

WHEREAS, presidents of the Maine Medical Association are operative in far reaching policy decisions during their terms of office, and

WHEREAS, they are privy to many matters of great importance to the M.M.A., and

WHEREAS, this knowledge could be of considerable help to the M.M.A. for more than the one year after office that they are presently Executive Committee members,

THEREFORE BE IT RESOLVED: That presidents of the M.M.A., whose terms of office expire in or after June, 1977, become, at their option, members of the Executive Committee for an additional period, not to exceed three (3) years, with all rights and privileges pertaining thereto.

**Nominations** — Presented by the Androscoggin County Medical Association, the resolution as submitted was defeated. A substitute resolution presented by the Reference Committee, which will require a change in the Bylaws, was *approved*:

MOVED: To amend the Bylaws of the Maine Medical Association, Chapter IV, Section 10 with the addition of "with the exception that nominations from the floor for an Executive Committee District representative shall be made by only the delegation from that District."

**Liability Insurance** — Presented by the Cumberland County Medical Society, this resolution *approved* as amended:

WHEREAS, members of the Maine Medical Association can no longer reasonably obtain professional liability insurance in the voluntary market, and

WHEREAS, the nonavailability of such insurance from voluntary companies has adversely affected the delivery of medical care in the State of Maine,

BE IT RESOLVED, that the M.M.A. will assume the leadership in seeking to resolve this crisis, including the study of the creation of a physician-directed insurance company, and that the responsibility for this action will rest with a committee to be appointed by the President, and

BE IT FURTHER RESOLVED, that the



ROCHE LABORATORIES  
Division of Hoffmann-La Roche Inc.  
Nutley, New Jersey 07110

committee is to be budgeted up to \$10,000. (Projected source of funds — M.M.A. reserve capital)

**Medicare Fiscal Intermediary** — Presented by the Cumberland County Medical Society, this resolution *approved* as amended:

WHEREAS, Union Mutual Insurance Company is terminating its contract as the financial manager of Medicare in Maine, and

WHEREAS, Union Mutual has been an available, cooperative and concerned company for the needs of Maine Medicare residents,

BE IT RESOLVED, that any company or organization chosen to replace Union Mutual be a Maine-based organization employing Maine people, so that communication between Medicare recipients, medical providers and this-to-be announced organization will result in continued high quality administration of Maine Medicare funds. The Maine Medical Association urges their legislators and the Federal Government to keep Maine Medicare administration in Maine.

The Maine Medical Association was further *instructed* to send a letter to this effect to HEW and the Maine Congressional delegation.

**Stillbirths and Neonatal Deaths** — Presented by the Committee on Maternal and Child Welfare, this was *approved*:

WHEREAS, there is good evidence that stillbirths and neonatal deaths are under reported in this State,

WHEREAS, it is necessary to make long-range plans for improving the perinatal facilities in the State of Maine, and

WHEREAS, there are pediatricians and obstetricians interested in gathering accurate data on infant deaths, neonatal deaths, stillbirths, and maternal high-risk pregnancies, morbidity and mortality, and formulating long-range recommendations based on these data,

THEREFORE BE IT RESOLVED, that the Maine Medical Association recommends that legislation be enacted to make it mandatory for weight and estimated gestational age to be entered on all stillbirth and neonatal death certificates (infants less than 30 days of age after birth), and

THEREFORE BE IT FURTHER RESOLVED, that a copy of this resolution be forwarded to the Legislative Committee and the legal counsel of the Maine Medical Association and to the Governor and Commissioner of Human Services of the State of Maine.

**Medical Examiner Law** — Presented by the Executive Committee, this was *approved*:

WHEREAS, the M.M.A. wishes to maintain high standards of professional activity, and

WHEREAS, the M.M.A. reaffirms the principle that physicians have legal and moral respon-

sibilities to their patients for meeting their medical needs including the certification of their death, except when the law requires such certification by a medical examiner, and

WHEREAS, the M.M.A. reaffirms that the certificate be signed within 24 hours as required by law, and

WHEREAS, the M.M.A. reaffirms that the physician's responsibility applies to all patients, including those of hospital-based specialists and to nursing home occupants; meaning, it should be the duty of the physician to view the body after death, either in the home, in the hospital, in the nursing home, or in the funeral parlor, wherever the appropriate place to ascertain the facts as to the reason for death, and

WHEREAS, the M.M.A. supports the principle that ethically death is a medical diagnosis, and while the fact of death may be temporarily assumed by others, i.e., police, nursing, and ambulance personnel, ultimately a licensed physician should, where feasible, examine the body and pronounce the reason for death, and

WHEREAS, no death should be certified without examination of the body unless such examination has been completed by a physician other than the certifier with whom the certifier has been in contact,

THEREFORE, BE IT RESOLVED, that all physicians familiarize themselves with the Medical Examiner Law and that the M.M.A. do all it can to provide physicians the impetus to properly carry out their responsibilities.

**M.M.A. Headquarters** — The original resolution from the Androscoggin County Medical Society was defeated. A substitute resolution, recommended by the Reference Committee was *approved* as follows:

MOVED, the Maine Medical Association, no later than January 1, 1980, acquire or rent buildings in Augusta, Maine, for the transfer of the headquarters of the Maine Medical Association to Augusta, Maine, by that date.

The resolution submitted by the Cumberland County Medical Society on the same subject was withdrawn in favor of the substitute resolution.

**M.M.A. and the Associated Hospital Service of Maine** — Presented by Dr. George Wood of Bangor, was *approved*:

RESOLVED, that the Committee on Health Care Financing re-examine the relations between the Maine Medical Association and the Associated Hospital Service of Maine, and report on this relationship and its recommendations at the April Interim Session in 1978.

**Smoking** — The following resolution, originally adopted by the House of Delegates on April 8, 1962, was *re-affirmed* at this meeting:

WHEREAS, the Maine Medical Association represents the medical profession of the State of Maine, and

WHEREAS, this Association is aware of its responsibilities toward the citizens of the State of Maine, and

WHEREAS, there is mounting evidence of a causal relationship between cigarette smoking and lung cancer, and

WHEREAS, no less a person than the Surgeon-General of the United States Public Health Service has noted this causal relationship, and

WHEREAS, it has been estimated that 1,000,000 of our present population of school children will die of lung cancer if present cigarette smoking trends continue

BE IT RESOLVED, that the Maine Medical Association, aware, as it is of its duty to alert the citizens of the State of Maine to public health hazards, wishes to acknowledge the causal relationship between cigarette smoking and lung cancer, and

BE IT FURTHER RESOLVED, that this Association desires to encourage the dissemination of information regarding the causal relationship between cigarette smoking and lung cancer.

A **resolution** submitted by Dr. Hartman, Alternate Delegate from Aroostook County, regarding **HR 6222** (Comprehensive Health Care Bill) lacked sufficient votes to allow consideration.

**Reports of Reference Committees** — Recommendations (not listed elsewhere in this summary) are as follows:

**Peer Review Committee** — As suggested in the Committee report, the Reference Committee recommended that the Executive Committee be instructed to formally explore ways to strengthen the relationship between the M.M.A. and the Pine Tree Organization and further, that the House of Delegates lend its endorsement to the PTO's efforts to recruit physicians as members in PTO as a visible expression of physician support for its peer review activities. This was *approved*.

**Journal Editor** — The Reference Committee recommended that the Executive Committee be directed to proceed in the hiring of an Editor for *The Journal of The Maine Medical Association*, and this was *approved*.

**Employment Policy and Benefits** — The Reference Committee recommended that the Assistant Executive Director be directed, under the guidance of the Budget Committee, to develop an employment policy, to define conditions for employment, benefits for all, including retirement benefits, not to exceed the budget. This was *approved*.

**Committee on Health Care Financing** — The Reference Committee recommended that the Commit-

tee on HCF be directed to continue to explore all avenues of assistance and cooperation with the Department of Human Services. This was *approved*.

**Committee on Conservation of Vision** — The Reference Committee recommended that the Executive Director of the M.M.A. be instructed to distribute a letter on the use of cortico-steroids, as developed by the Section on Ophthalmology of the M.M.A., to members of the M.M.A. and other interested parties. This was *approved*.

**School Health Committee** — The verbal report was accepted, and the Reference Committee recommended increased participation of physicians in school health. This was *approved*.

**A. H. Robins Community Service Award** — The award for 1977 was presented to Dr. Robert O. Kellogg of Bangor.

**Maine Blue Cross and Blue Shield Award of Appreciation** — This year's award was presented to Dr. Dexter E. Elsemore of Dixfield.

**Out-of-State Delegates** — The following delegates spoke briefly of the major problems in their respective states and extended greetings on behalf of their Associations: Dr. Bernard O. Nemoitin, Connecticut; Dr. Robert Conrad, Rhode Island; Dr. Theodore Smith, New Hampshire; and Dr. B. Albert Ring, Jr., Vermont.

**Health Systems Agency** — Dr. Richard Swengel, a member of the Board of HSA, spoke of its activities and of bills currently being considered by the legislature that are of concern. He urged that each physician become informed about the HSA's purposes and objectives.

**Maine Association of Medical Assistants** — Ms. Betsy Whitcomb explained what a "medical assistant" is and does, stated the goals and purposes of the M.A.M.A., and urged that physicians lend support to them.

**AMA Delegate** — Dr. Robert E. McAfee explained his duties as AMA Delegate and as chairman of the New England delegation. Dr. McAfee invited response from our members on issues that are to be considered at the upcoming AMA convention.

**Medical Care Development, Inc.** — Dr. Manu Chatterjee, with the aid of slides, explained what MCD is and what it does. It is a not-for-profit corporation governed by a Board of Directors. The major emphasis of MCD has been on experiments in new methods of delivering health services. There are currently several that it has been closely involved in, Dr. Chatterjee said. The development of new health manpower is an important phase of the total

*Continued on Page 400*

# County Society Notes

## Washington

A regular meeting of the Washington County Medical Society was held on May 5, 1977 at the Stable Inn, Calais, Maine, with twenty-three members and guests present.

Following the dinner at the Stable Inn, the members and their wives retired to the home of Hazen and Katrine Mitchell in Calais, Maine, where members of the Washington County Medical Society held a business meeting. Dr. G. Bernard Shaw, President of the Society, presided.

The first item of business was a discussion of Bangor Mental Health Institute. Dr. John Healey, Psychiatrist at the Eastern Maine Medical Center and at the Bangor Mental Health Institute, spoke in regard to BMHI. He stated that recently fifteen psychiatrists from the northeastern part of Maine held a meeting. Their opinion was that Bangor Mental Health Institute, particularly the acute care section, should be kept in operation. He felt this was very important for the whole northeastern part of Maine. He also emphasized the importance of having a Medical Center adjacent to the Bangor Mental Health Institute. Many specialists have been attracted to Bangor and there has been increased cooperation between Bangor Mental Health Institute and the Eastern Maine Medical Center, particularly the psychiatric section and the medical section.

Motion was made and passed that *Washington County Medical Society go on record that closing of the BMHI would be a distinct step backward in delivery of psychiatric care in northeastern Maine and that referrals and admission to BMHI be under psychiatric control.*

The Society also felt that we would like to be able to refer patients there, as we have done in the past. It was also stated that this resolution be sent to the Committee on Institutional Service of the State Legislature and to the members of the Legislature of Hancock and Washington Counties.

Next on the agenda was a discussion of the Washington County Health Plan. Dr. Donald M. Robertson, President of the Washington County Health Plan, said that we had three alternatives:

- 1) Refuse any change.
- 2) Adopt new bylaws.
- 3) Set up a new, complete re-organization with grant monies to be obtained through R.M.C.L., Lubec, or through the County Commissioners or the Municipal Officers Association, etc.

It was so felt that the Washington County Medical Society would start a foundation to run the Washington County Health Plan.

Motion was made that the Washington County Health Plan be discontinued. This was not seconded.

Motion made and seconded that we recess and re-convene in two weeks, to reconsider the W.C.H.P. with the meeting held preferably in Dennysville, Maine on Friday, May 20, 1977. It was so voted.

A letter was read from Dr. Martyn Vickers, Jr. who is a candidate for President of the Maine Medical Association. Dr. Richard C. Leck, Bath, Maine, President of the Maine Medical Association, was present at the meeting and commented on this letter, stating that there were various candidates for the office of President and that this will be settled in June at the annual meeting of the Maine Medical Association. Dr. Leck also spoke on other matters facing the Association and also of L.D. 727, which he said all M.D.'s should support and have it passed in its entirety.

Meeting adjourned at 1:30 a.m.

A regular meeting of the Washington County Medical Society was held on May 20, 1977 at the Lincoln House, Dennysville, Maine, with nine members present.

### I. FIRST ORDER OF BUSINESS:

A certificate of need for Eastport for a National Health Service Corp physician was moved, seconded and passed. A letter to be sent to Dr. James C. Bates, Eastport, Maine stating that Washington County Medical Society at their regular meeting on May

20, 1977 approved the need in Eastport for a National Health Corp physician.

### II. ELECTION OF OFFICERS:

President: Dr. James C. Bates, Eastport

Vice-President: Dr. Richard J. Forsyth, Woodland

Secretary-Treasurer: Dr. Karl V. Larson, East Machias

Board of Censors: Drs. John Kazutow, Columbia Falls, Hazen C. Mitchell, Calais and Rowland B. French, Eastport

Delegate to the M.M.A. House of Delegates: Dr. Robert G. MacBride, Lubec. Alternate: Dr. Donald M. Robertson, Milbridge

A rising vote of thanks given to Dr. G. Bernard Shaw of Machias, Maine, who served as President for the past eight years. Meeting then turned over to Dr. James C. Bates, Eastport, Maine, incoming President.

### III. DISCUSSION OF WASHINGTON COUNTY HEALTH PLAN:

Dr. Robert G. MacBride, Lubec, Maine read a letter expressing his thoughts. He stated that the program should cover all parts of Washington County, for all of its consumers and providers, by so doing we would achieve a common goal of better health care for people. The County Society agreed with the Federal Guidelines, which include 51% consumer representation on the Board of Directors. A seventeen member board was suggested, nine of whom would be consumers, eight would be providers. Four of these professional medical members on the board to be appointed by the Washington County Medical Society. The Medical Society was in general agreement as to the need for a Consumer Health Center grant, Migrant Workers Center grant and Rural Health Initiative grant. They felt that practice management should be eliminated and they also felt that the fee schedule for the Eastport Dental Clinic should be re-evaluated. The Washington County Medical Society also felt that the Board of Directors and the Executive Directors of Washington County Health Plan had not implemented the recommendations of the auditors.

A regular meeting of the Washington County Medical Society was held on June 2, 1977 at the Lincoln House Country Inn, Dennysville, Maine, with ten members present.

I. Meeting opened under the direction of Dr. James C. Bates, President, of Eastport, Maine.

II. Minutes of last meeting read and approved.

III. *New Business:* It was moved, seconded and passed, that any issue requiring a vote of the members, would be by ballot of members.

IV. *Old Business:* Discussion of Washington County Health Plan, particularly the last meeting of the WCHP, and the results of that meeting, held at the Down East Community Hospital, Machias, Maine. Discussions by Drs. Robert G. MacBride of Lubec, Maine and John Kazutow, of Columbia, Maine.

**F.P.'s NEEDED** — Growing comm. of 4000+ needs 1-2 M.D.'s. 2 F.P.'s in town & 1 nearby. Join exist. prac. or solo avail. Xln't rec. & econ. 60 mi. from metro-cities, 57 Bed J.C.A.H. Hosp. in comm. Trade area of 12,000+ U.S. Grad. pref. Contact L. Wattier, Adm., Mem. Hosp. Inc., 104 W. 17th St., Schuyler, NE 68661 (402) 352-2441.

V. Dr. Bradley E. Brownlow, a member of the Board of Trustees of the Health Systems Agency, spoke in regard to the Agency and its plans for the future. He discussed the upcoming "Certificate of Need" legislation, stating the Dept. of Human Services had one bill that was backed by the Maine Medical Association and that the Health Systems Agency had another bill, and the main differences were that the Health Systems Agency would require all components of the health group to come under surveillance whereas the Dept. of Human Services' bill would exclude certain groups, such as physicians' offices, mental health groups and other small units. Dr. Brownlow felt

that the physicians should be included in the "Certificate of Need" legislation, since that if they were excluded now, surely, within two years' time it would be necessary to include them, since the general public would wonder why the physicians' offices should be treated any differently than any other part of the health team. Dr. Brownlow said that there were three components of the M.H.S.A.: 1) Administration, 2) Project Supervision, and 3) Future Planning (of which he was chairman).

Dr. Brownlow showed us a large two and one-half pound manual of which he said covered the future planning.

KARL V. LARSON, M.D., *Secretary*

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FROM THE SECRETARY'S NOTEBOOK — *Continued from Page 398*

program, with a major interest now in continuing education. Dr. Chatterjee also spoke about the "compacts" the State of Maine has with various medical schools.

**Legislation** — Charles L. Cragin, III, Esq., lobbyist for the Maine Medical Association, spoke at length on a variety of legislative topics, among them Malpractice, the JUA, Certificate of Need, Rate Review Legislation for Hospitals, the Nurse Practice Act, Brain Death and Living Will, Medical School Compacts, Board of Registration Funds, Authority to Regulate Health Care Facilities, Prescription Blanks, and the Patient's Bill of Rights.

**Special Memberships** — The recommendations by

the county societies for special memberships were approved.

**Stenographic Record** — A summary of the proceedings of the House of Delegates is to be sent to county presidents and to the members of the House of Delegates. (The complete transcript is on file at the Association's office in Brunswick, where it is available for examination by any member of the Association.)

The meeting was recessed at 5:15 P.M. on Saturday, June 11, and was adjourned at 4:30 P.M. on Sunday, June 12.

PATRICIA A. BERGERON  
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# The Journal of the Maine Medical Association

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Number 11

## The Role of the Emergency Department in the Delivery of Rural Primary Care

DAVID WILNER\*

This report is an analysis of the Emergency Service Department (ESD) of the Stephens Memorial Hospital in Norway, Maine. The survey was done to answer the question of whether the emergency department of a rural hospital is serving as a source of primary care to patients. If primary care is defined as a medical program which provides the initial assessment and initial treatment of a patient's medical needs, a trend towards this type of care, as opposed to acute lifesaving treatment, has been well-documented in urban emergency departments.<sup>1,2</sup>

The Stephens Memorial Hospital is located in the towns of Norway and South Paris, Maine, and serves an area of about 375 square miles located mainly in Oxford County. The hospital's primary service population is defined as Norway, Paris, and six surrounding towns having in 1973 a combined population of 13,600. An additional seven towns shared with other hospitals as a secondary service population comprises 8,800 more people.

The hospital is a 41-bed hospital which includes a four-bed Special Care Unit and a four-bed maternity unit. It is currently undergoing an expansion of its physical plant which will enlarge and update its facilities. Neighboring hospitals include two hospitals in Lewiston (25 miles east) each of 250 beds, four hospitals in Portland (50 miles south) including the Maine Medical Center, one eighty-bed hospital in Rumford (40 miles north) and a forty-bed hospital in Bridgton (20 miles west).

The hospital staff consists of 17 physicians. This includes 6 general practitioners, 2 general surgeons, one orthopedist, 3 internists, 2 emergency medicine physicians, 2 radiologists (providing full-time coverage of one radiologist), and a pathologist. Almost half of these physicians are under 40 years of

age and have joined the staff in the last two years. This helped lead to a dramatic increase in the quantity and quality of medicine practiced in the community with the result that more and more area residents are remaining within the community for their medical needs, rather than going to a neighboring larger community.

### METHODS

This study consists of a retrospective and a prospective examination of patients using the ESD. The retrospective study consists of a review of 617 patients' visits over the period June 1, 1975 to May 31, 1976 (total visits: 12,842). The ESD log was used to select systematically the visits to be looked at and information was gathered from the corresponding medical record. The prospective study is a compilation of data from interviews conducted with patients when they came to the ESD for treatment. The patients were selected at random. A total of 105 patient visits were used in this study.

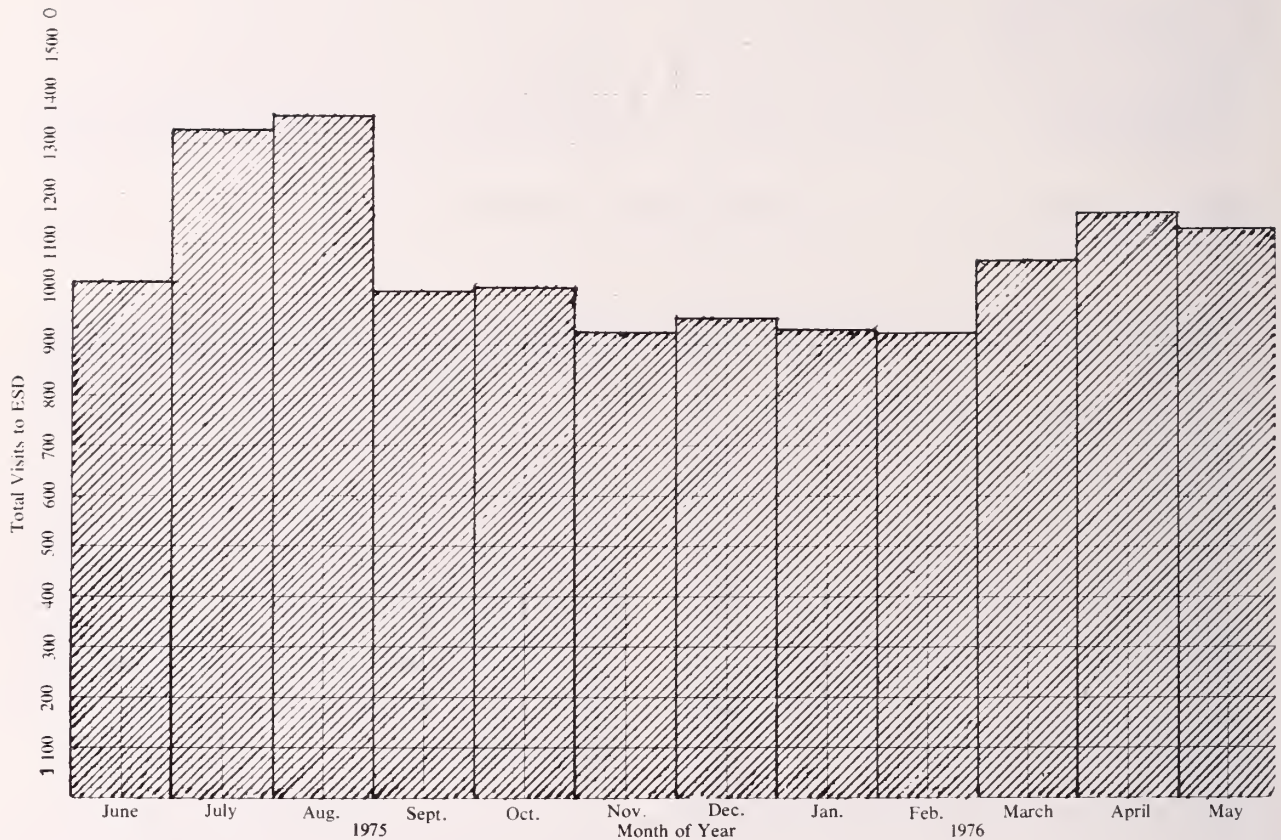
### THE EMERGENCY SERVICE DEPARTMENT

The ESD is normally staffed by 2 nurses during the day shift, 1 nurse during the evening shift, and is covered by the floor nurse during the night shift. The hospital currently employs 2 physicians (only 1 prior to July 1, 1976) who work exclusively in the Emergency Service Department, staffing the ESD from 8:00 a.m. till 6:00 p.m. on weekdays and for 24-hour shifts on the majority of weekends. The rest of the time is covered by required rotations of the physicians on the hospital's active staff. The physician on call is required to stay on the hospital grounds so that a physician is always present when needed in the emergency room.

The use of the ESD has climbed dramatically over the past years. In 1968, there were 5,200 visits; in

\*Student, Tufts University School of Medicine.

Graph 1  
Utilization by Month of Year



1970, 7,150; in 1972, 9,300; in 1973, 10,900; in 1974, 11,700; and in 1975, 11,770. The population of the service area has not grown nearly as fast: in 1960, gross population was 20,300; in 1970, 20,960; and in 1973, the population reached 22,425.

## RESULTS

### Monthly Utilization Rate (see graph 1):

This data is presented as total number of patients seen each month. A seasonal fluctuation in use of the ESD can be seen. The heaviest use is in the summer months. This is partially related to the influx of summer people into vacation homes, camping areas, and children's camps. Since these people do not have family doctors in the area, they primarily use the ESD for their medical needs. In addition, the summer months are favorite times for the area physicians to vacation, thus sending more people to the ESD. During the 12 months covered by this study, 12,842 visits to the ESD were recorded.

### Diagnoses:

Patients' diagnoses were divided into several classes as seen in Table 1. Major burns cover greater than 2% of the body area; major lacerations involve subcutaneous suturing; major abrasions cover large areas of the body. Minor burns, abrasions, contu-

TABLE 1

DIAGNOSES	retrospective		prospective	
	#/617	%	#/105	%
Trauma:				
Minor burns, abrasions, contusions, lacerations	151	24.5	24	22.8
Major burns, abrasions, contusions, lacerations	31	5.0	7	6.7
Fractures	38	6.2	1	0.9
Other orthopedic	69	11.2	12	11.4
Eye trauma	20	3.2	1	0.9
Medical:				
EENT diseases	74	12.0	13	12.4
Cardiovascular	22	3.6	5	4.8
Major respiratory	25	4.0	3	2.8
Minor respiratory	24	3.9	5	4.8
Gastrointestinal	45	7.3	3	2.8
Genitourinary	12	1.9	3	2.8
Other infectious diseases	21	3.4	2	1.9
Other infections	26	4.2	10	9.5
Dermatologic and Allergic	32	5.2	10	9.5
Other	25	4.0	4	3.8
Psychiatric	10	1.6	2	1.9

sions, and lacerations include all those not classified as major and this is the category with the largest percentage (22.8%) of patients. Diseases of the eye, ear, nose, and throat were the second largest group of patient complaints, amounting to 12% of the total.

TABLE 2

SERVICES RENDERED	Retrospective		Prospective	
	#/617	%	#/105	%
Exam only with advice	138	22.4	24	22.8
X-Rays	128	20.7	21	20.0
Dressing wounds, applying bandages (includes ace)	114	18.5	24	22.8
Minor surgery	71	11.5	12	11.4
Laboratory	65	10.5	3	2.8
Electrocardiogram	20	3.2	3	2.8
Casts or splints	18	2.9	0	0
Cardiorespiratory Support	1	0.2	0	0
I.V. Fluids	1	0.2	1	0.9
Medications given	264	42.8	57	54.3

Other orthopedic diseases refers to ligament tears, muscle and tendon pulls, and inflammation. Major respiratory diseases were asthma, pneumonia, and bronchitis while minor respiratory diseases were upper respiratory infections.

By separating the classes into trauma and medical cases, it is seen that visits are divided evenly between the two. One might think that the majority of medical cases could easily be seen in a doctor's office, as well as some of the trauma cases.

Of the 105 patients interviewed in the prospective study, similar results are noted with the exception of a decrease in fractures, and an increase in infections, dermatologic and allergic diseases. A high percentage of this latter class is comprised of people seeking treatment for insect bites.

#### *Services Rendered:*

The services performed for a patient may be considered as an indicator of the gravity of the problem. As seen in Table 2, patients coming into the ESD were categorized as to services given them; many received services in more than one category. The fact that 22-23% of the patients in both studies received only advice from the duty doctor might suggest that these patients' complaints were not considered urgent by the physician. Similar percentages of patients in both studies were sent to x-ray but a marked reduction in use of the lab facilities in the prospective study is noted. The category of minor surgery includes suturing, removal of foreign bodies, debridement of wounds, and incision and drainage of lesions; 11% of patients had one of these procedures performed. The critical lifesaving procedures of cardiorespiratory support and administration of intravenous fluids were not performed often in the ESD. However, these figures may not reflect the number of patients coming through the ESD who require this treatment since many such patients are admitted directly to the Special Care Unit. A very large percentage of people coming to the ESD either receive medication in the ESD or leave with a prescription for medication.

#### *Source of Referral to the ESD:*

If an Emergency Department is used for primary

TABLE 3

SOURCE OF REFERRAL	Retrospective		Prospective	
	#/617	%	#/105	%
Recheck	70	11.3	9	8.6
Self and Relative			90	85.7
Physician	547	88.7	5	4.8
Other			1	0.9

TABLE 4

MODE OF ARRIVAL	Retrospective		Prospective	
	#/617	%	#/105	%
Ambulance	30	4.9	2	1.9
Nonambulatory	20	3.2	3	2.8
Ambulatory	566	91.7	100	95.2

care medicine, one would expect a large proportion of patients to be referred to the ESD by themselves or by relatives. In the prospective study, it can be seen in Table 3 that 86% of all patients were self or relative referred. Only 5% stated that they had spoken to or seen a physician who referred them to the ESD, whereas 9% of patients were coming back to the ESD for a recheck of a problem already seen and treated by a doctor. In the retrospective study, it was only possible to differentiate rechecks from all other sources of referrals. Almost 89% of patients were coming in for initial treatment and 11% of the visits were for rechecks. The physicians employed by the hospital are not supposed to follow patients over the course of an illness. They do remove sutures, change bandages, etc., but they refer most patients to a family doctor for followup. It is likely that many patients who, having been referred to a family doctor, still come back to the ESD.

#### *Mode of Arrival (Table 4):*

In the retrospective study, 5% of patients were brought to the ESD by ambulance or rescue unit. The 3% figure for patients who were nonambulatory is questionable since this was based on an interpretation of a patient's condition from the medical record by the author. Almost 92% of patients were able to walk into the ESD. In observing patients over the summer, 2% came by ambulance, 3% were nonambulatory, and 95% were ambulatory.

#### *Disposition and Followup (Table 5):*

Of the records examined retrospectively, 58.5% of the patients were sent home from the ESD with no further visits to a doctor needed, 9% of patients were scheduled to come back to the ESD to be rechecked and 22% were sent home and told to make an appointment to see their private physician. Only 6.8% of patients were admitted to the hospital as a result of their assessment in the ESD. A small number of patients, 2.3% were sent to another doctor for initial treatment of their medical problem; most of these cases were orthopedic. Only 0.5% of

Graph 2  
Utilization by Day of Week

Percentage of Visits

8%  
6%  
4%  
2%  
0%  
8%  
6%  
4%  
2%

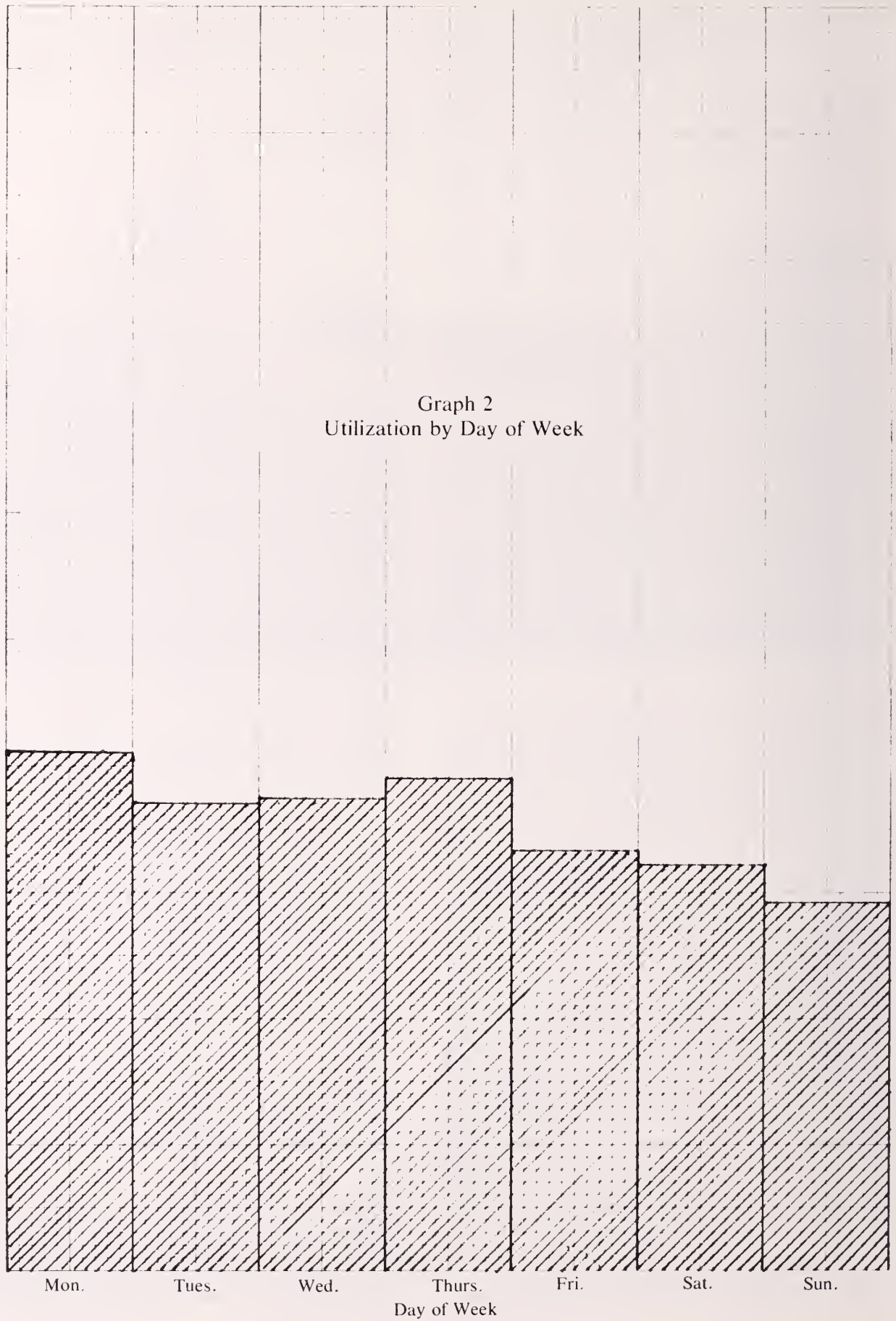


TABLE 5

DISPOSITION AND FOLLOWUP	Retrospective		Prospective	
	#/617	%	#/107	%
Sent home	361	58.5	69	65.7
Sent home with return scheduled to ESD	56	9.0	6	5.7
Sent home with return to private physician	137	22.2	21	20.0
Referred to specialist for initial treatment	14	2.3	3	2.8
Admitted to hospital	42	6.8	6	5.7
Transferred to another hospital	3	0.5	0	0

patients required treatment not available at Stephens Memorial Hospital; they were transferred to larger hospitals. These cases were largely neurological in nature. Similar figures are seen in the prospective study. Only 8.6% of the patients included in the current study were sent home without written instructions. The hospital medical audit committee had requested all doctors to give patients using the ESD written instructions as of June 1976.

#### Age of Patient (Table 6):

It can be seen in the corresponding table that there

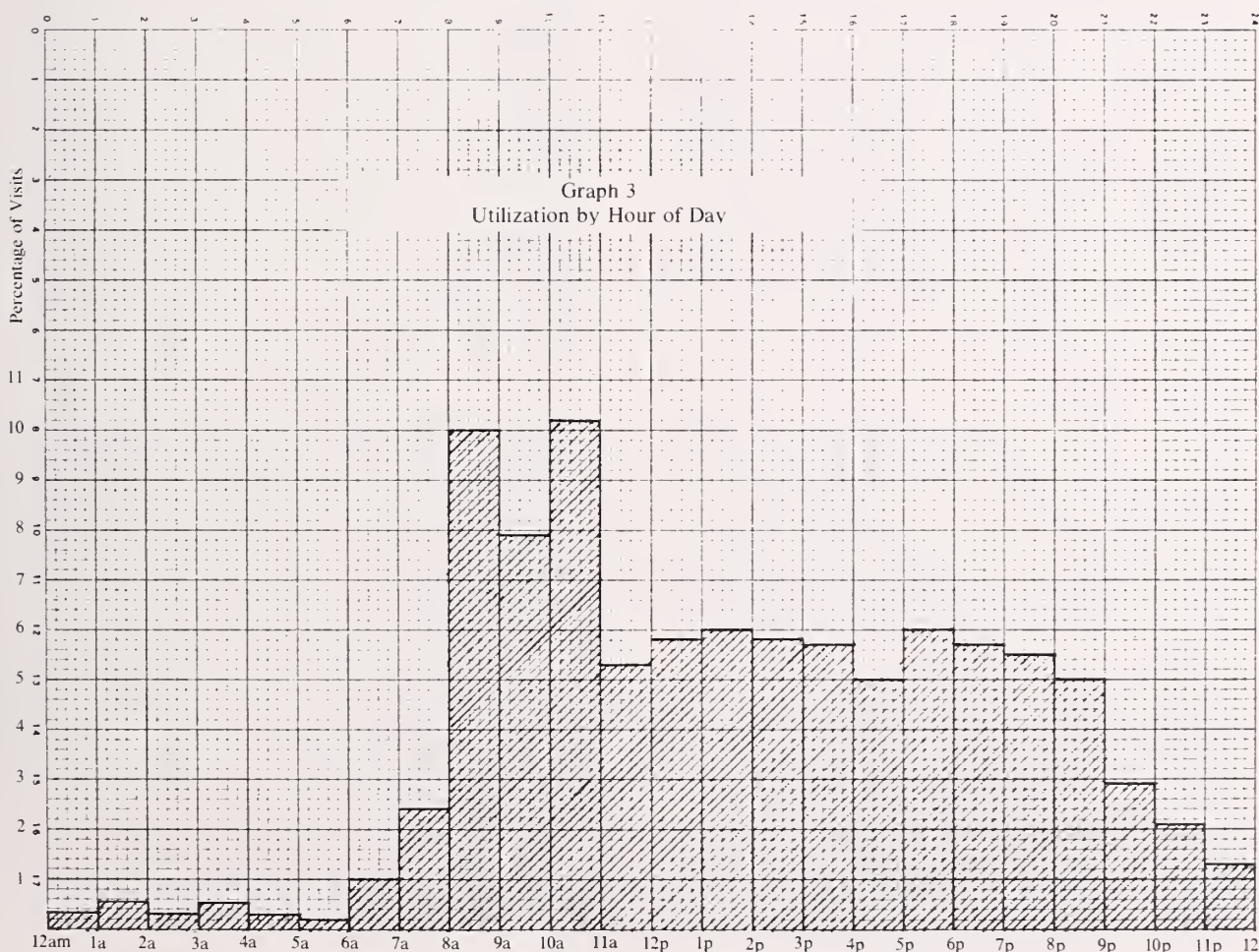
TABLE 6

AGE OF PATIENTS USING THE ESD	Retrospective		Prospective	
	#/617	%	#/105	%
0-2 years	41	6.6	7	6.7
3-13 years	137	22.2	26	24.8
14-21 years	117	19.0	24	22.8
22-50 years	207	33.5	24	22.8
51+ years	103	16.7	22	20.9

is a large percentage of young people using the ESD facilities. Almost one-third of all patients were 13 years old or under, and approximately one-half of all patients were 21 years old or under. Data on age distribution within the population served by the hospital, based on the 1970 census, shows that 28% of people were 5 years old or less, 44% were 24 years old or less, leaving 56% over 24 years old.

#### Utilization by Day of Week:

In the accompanying graph (#2), visits per day of the week are plotted as a percentage of the total visits. Monday is the busiest day of the week and Saturday and Sunday are the least busy days of the week. Wednesday, which is the day four of the six general practitioners take off, is not particularly differentiated from Tuesday or Thursday.



### Utilization by Hour of Day:

A large percentage of visits take place during the hours when physicians' offices would be open if it were during the weekday. As seen in the corresponding graph (#3), there was a peak of activity from 8:00 a.m. till 11:00 a.m. followed by a steady number of visits through the early evening. A decline in visits occurs throughout the late evening to reach a minimal level from midnight till 6:00 a.m.

### Emergency or Not Emergency (Table 7):

In the retrospective study, every tenth record from the original sample of 617 records was selected to comprise a total of 61 patient visits. Three physicians (an internist, a general practitioner, and an emergency service department physician) were asked to look at each of these records and independently grade them into one of three categories 1) Should be seen by a physician within 24 hours and requires the facilities of the ESD. 2) Should be seen by a physician within 24 hours but could be seen in a doctor's office. 3) Does not require a doctor's attention within 24 hours. At least 2 of the physicians concurred in saying 38% of these cases fit into the first category — should be seen by a doctor within 24 hours and required the facilities of the ESD, 49% of patients could easily be taken care of in a doctor's office but needed to be seen within 24 hours. At least 2 physicians felt that 13% of the patients did not have to be seen within 24 hours.

The same classification system was used in the prospective study when the duty doctor was asked to rate each patient into one of the three categories. Of the 105 patient visits examined, 21% were felt to require their attention within 24 hours and also required the ESD facilities. Another 20% of patients were felt to need a doctor's attention within 24 hours but could have been taken care of in a doctor's office, and 60% of patients were not felt to need medical attention within 24 hours.

### Source of Payment:

It can be seen in Table 8, that the majority of patients listed a potential third-party payer. About 11% of patients were covered by workmen's compensation, thus indicating industry-related accidents. Prior to the staffing by physicians of the ESD, most of the companies sent all accident victims to a doctor's office. Now the practice is to send such people to the hospital's ESD.

### Geography:

From Table 9, it can be seen that 73% of patients come from the primary service area of the Stephens Memorial Hospital, 15% come from the secondary service area, 5.5% come from out of state (mostly tourists) and 6% come from other Maine areas. This last category consists of those patients in another hospital's service area who use Stephens Memorial Hospital on a regular basis by personal choice, and those who are transients or tourists.

TABLE 7

	EMERGENCY OR NOT EMERGENCY			
	Retrospective		Prospective	
	#/617	%	#/105	%
Within 24 hours — ESD	23	37.7	22	20.9
Within 24 hours — office	30	49.2	21	20.0
Not within 24 hours	8	13.1	62	59.1

TABLE 8

	SOURCE OF PAYMENT			
	Retrospective		Prospective	
	#/617	%	#/105	%
Medicare/Medicaid	127	20.6	19	18.1
Compensation	71	11.5	11	10.5
Blue Cross/Shield	163	26.4	18	17.1
Other Private Co.	129	20.9	26	24.8
None listed	104	16.9	26	24.8
Other source of payment	21	3.4	0	0

TABLE 9

	Retrospective	
	#/617	%
GEOGRAPHY		
Primary Service Area:		
Greenwood	6	1.0
Norway	160	25.9
Oxford	51	8.3
Paris	151	24.5
Stoneham	5	0.8
Sumner	8	1.3
West Paris	41	6.6
Woodstock	27	4.4
Secondary Service Area:		
Bethel	25	4.0
Buckfield	21	3.4
Hebron	11	1.8
Harrison	10	1.6
Mechanic Falls	15	2.4
Otisfield	3	0.5
Waterford	9	1.5
Other Maine Areas	37	6.0
Out of State	34	5.5

### DISCUSSION

The most interesting data to examine are the facts of whether a patient's problem is emergent, and whether they have a family doctor. In the former category, a disparity exists between the retrospective and the prospective study. Since other categories of the two studies were only slightly different (specifically the diagnosis and services rendered categories), a major difference between the two studies in percentage of patients considered presenting with emergent cases was not expected. Several points can be made. The first consideration is that these might both be accurate representations of the patients seen in the two studies. Since most of the prospective study was done during the day with fewer patients interviewed in the evening and none during the late night, it might be argued that a large percentage of emergent cases (most of those normally seen late at night) were missed, thus more non emergent cases were picked up. One might consider

the prospective study to be more accurate in considering whether a patient's problem is emergent. Certainly the physician has more information available to him than does the physician grading the medical records in the retrospective study. It could also be argued that the physician on call is less accurate than the physician examining a record retrospectively because he might be harried by a large number of patients in the ESD. In such a situation, the doctor might be inclined to say that a patient's visit was not emergent (did not need to be seen within 24 hours); while under calmer conditions, he might agree that the patient warranted examination within 24 hours. It is interesting to note that in a similar study of an urban emergency room,<sup>3</sup> a similar variance was seen between a prospective and retrospective study.

A problem with the current study question of whether a person has a family doctor is that the summertime is not typical of the remaining 9 months of the year. Summer is the time that many physicians take vacations. In addition, there are many summer visitors in the area. Both factors contribute to an increased use of the ESD facility. If the two groups of patients representing these factors are removed from the study, slightly different results are found. This would be an assumption, not necessarily valid, that those physicians who were away could have taken care of their patients who called, either by talking to them or by seeing them in their office. In this case, a larger number of patients (62%) coming to the ESD are found to have a family doctor, but only 1/4 of these called their doctor; 3/4 of patients not having a family doctor had no special reason for not having one. In addition, 52% of patients, as opposed to 59% before the revision of the figures, were said by the duty doctor not to need a doctor's attention within 24 hours; 26% of patients required the facilities of the ESD within 24 hours (previously 21%), and 22% should be seen within 24 hours but could be seen in a doctor's office (previously 20%).

An obvious conclusion to be drawn from all these figures and from talking with the physicians in the community, is that there are not enough general practitioners in town. In the retrospective study, only 38% of patients appropriately used the ESD and in the prospective study, only 26% of patients were determined to need the facilities of the ESD. This leaves the vast majority of patients, 62% in one study and 74% in the other, who could be taken care of in a physician's office. As seen in the daily and hourly utilization charts, the busiest days and hours in the ESD are the same times the physicians are in their offices. Therefore, a large percentage of patients coming to the ESD could theoretically be cared for by a private physician in his office. Practically, however, there are several reasons why patients come to the ESD.

One reason is that those that have a family doctor often cannot get in to see their doctor when they

wish to be seen. Of the four general practitioners with the largest practices, one states that he leaves some time open during the day specifically for his patients who call that day. The others try to see as many of their patients who call as possible, but are limited to cancellation times and other rare extra time. All of the general practitioners can usually see a patient within 2 days but many patients insist on seeing a doctor earlier, even though they might have talked with their family physician, and the doctor determined they could wait to be seen. Although 13% of patients in the retrospective study and 52% of patients in the prospective study were judged not to need a doctor's attention within 24 hours, it is reasonable to assume that a majority of these patients probably felt that they should see a doctor within 24 hours. For those whose doctors cannot see them when they want to be seen, the ESD physician is available at any time of the day or night.

For patients who have no family doctor, the most common reasons heard were that the patient "seldom got sick," or that they "could never see a family doctor when they got sick." Most general practitioners in this area, since their practices are so busy, will not see a person with a complaint on short notice if it is not their own patient or the patient of a doctor for whom they are covering. That leaves a patient with no family doctor. It is thus hard to establish oneself with a family doctor since one primarily tries to do this when he is sick. If the desired goal is to align every person with a family doctor, then an ideal way to do this is to direct a patient to a general practitioner when they seek medical attention at the ESD. In the past, when there were two additional family doctors in the area, non emergent and emergent patients who could be seen in a doctor's office were often directed to a doctor's office where they could be seen the same day. Evidently, this was well accepted by most patients, and those patients who still wished to be seen in the ESD were accommodated. With the addition of more general practitioners to the community, for which a recruitment program is currently going on, this practice could be reinstituted.

Much of this discussion has promoted the referral of non emergent patients and those emergent patients who could be seen in an office, out of the ESD and into the care of a family doctor. This premise is based on two beliefs. One is that patients able to be taken care of by a family physician are likely to receive better total care, because of continuity of care, better knowledge of the patient by the physician, and a better understanding of the doctor by the patient. Second, overburdening the ESD with cases treatable by physicians in their offices, is an inefficient use of the facilities of the ESD. With the rapid trend towards greater use of the ESD as an outpatient clinic, illustrated by increasing usage over the years faster than the population growth, the manpower facilities will soon be overtaxed and unavailable to the people needing them.

In employing full-time emergency department physicians, the hospital is supplying, in effect, additional general practitioners for the community. Since these physicians are readily available, continued use of the ESD by persons with complaints treatable in an office is to be expected since these patients often feel they need immediate medical attention and are unable to get to or wait for their family physician. In addition, the ESD will almost certainly continue to serve as a primary care center during physicians' off-hours, a service highly appreciated and desired by the area physicians. Ideally, a patient treated in the ESD should be referred to a family doctor for any further medical care. This has the effect of establishing a patient with a family doctor if he did not already have one. Except for suture removal and bandage changing, this referral is usually made. However, a large number of people prefer to come back to the ESD, just as they came to the ESD for their initial visit. Since it is the policy of the hospital to treat all patients who come to the ESD, these patients will continue to use the ESD as a primary care facility. This policy is desirable from a consumers point of view since it allows one a choice of medical services. From a strictly medical point of view, however, patients should be established with a family physician. A combination of the two views would have the patients directed to and encouraged to use a family physician while still allowing unrestricted access to the ESD.

### CONCLUSIONS

A comprehensive examination of patients' visits to a rural emergency room has been performed retrospectively and prospectively at the Stephens Memorial Hospital. This hospital is typical of a good rural hospital and the results of this study can be extrapolated to the general question of the role the rural ESD plays in delivery of primary care in rural areas.

It has been found that a majority of patients using the ESD do not require the facilities offered. However, many of these patients do require a physician's attention within 24 hours. Since private physicians in the community can evidently not accept a large increase in patient load, the ESD seems to be performing the services of both an outpatient clinic and of an emergency room. There does not appear to be enough utilization at the present time to warrant setting up two separate units to fill these functions. Yet, if future use of the ESD increases as it seems to be doing, it will soon need expansion. The presumed alternative seems to be an increased number of general practitioners in the community with direction of more people to a family doctor.

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3. Jacobs, A. R., et al: JAMA: 216, 307-312, 1971.

## Tablets Percocet®-5

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**INDICATIONS** For the relief of moderate to moderately severe pain.

**CONTRAINDICATIONS** Hypersensitivity to oxycodone or acetaminophen.

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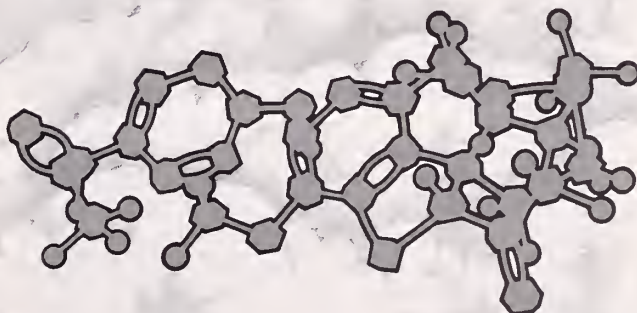
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# The General Internist is Alive and Well

WILLIAM L. MEDD, M.D. and DONALD E. WARE, M.D.\*

## ABSTRACT

Over the past several years there has been a growing controversy as to the role of the general internist in the delivery of medical care. Having completed eighteen months of private practice in internal medicine, we have concluded that the general internist is well equipped to be a primary care physician, as well as a hospital-based physician who carries on diagnostic procedures, does consultative work, and takes care of acutely ill patients. The best training for a practicing general internist is a four-year program with two years of general medicine and two years of subspecialty medicine; the latter should include at least six months of in-depth experience in one of the subspecialties. In choosing his practice, the general internist should strongly consider areas where there is a lack of his specialty. If he chooses an appropriate area, he will be able to use the skills and training that he has received to a maximum. He will find his practice experience to be a rewarding and challenging one as he fulfills a community need.

The excitement and challenge of our private practice pressure us to communicate our own prejudice regarding the role of the general internist. We firmly believe that the general internist plays a valuable role in the delivery of health care. Central to that thesis is our firm belief that comprehensive and sophisticated medical care should be delivered in the patient's locale where community resources, family and friends can be mobilized for care and rehabilitation of the patient. Because of these feelings, we have established our practice in a small rural town in Maine. With eighteen months of practice behind us, we should like to answer the following questions: 1) what type of training is most beneficial to an internist practicing in rural America? 2) what aspects of our community proved most conducive to the practice of good internal medicine? 3) what features of our own practice have proved most helpful in delivering good care? 4) what may an internist expect to see and do in rural practice? 5) what is the sacrifice, in an academic sense, when one leaves the urban areas and university hospital setting?

In considering the first question, we advocate four years of training in internal medicine. The first two years should be comprised of ward medicine, experience in intensive care medicine, emergency room medicine and longitudinal experience in out-patient clinics. The second two years should then be spent in two- or three-month rotations through medical subspecialties with a six-month block in a sub-

specialty of particular interest. This concept is in agreement with that of Dr. Petersdorf.<sup>1</sup>

We each took an internal medicine internship and first year residency at the University of Rochester. One of us went to Emory University in Atlanta, Georgia for six months of clinical cardiology and eighteen months of rotating subspecialty training. The other went to the University of Colorado for nine months of hematology and oncology and one year of rotating subspecialty training. Given this training and our own practice experience, we find that there are three general areas vital to the training of a general internist, areas which cannot be substantially augmented with postgraduate medical education in later years. Extensive experience in the care of critically-ill patients, exposure to a wide range of disease entities with an attendant development of diagnostic acumen, and sound training in the performance of procedures done in internal medicine are of paramount importance to the practice of rural internal medicine. In short, the rural internist must be a diagnostician and a good clinician, and he must develop these skills during his residency years. We feel that the only deficiency in our training years was the out-patient clinical experience. It was limited to one afternoon per week in a medical clinic. While we would not advocate more time spent in this area, we would have welcomed more experience in out-patient gynecology, minor surgery and surgical subspecialty problems.

With reference to the second question, there are many aspects of our community of Norway, Maine, which we find very conducive to the practice of good internal medicine. An obvious first consideration is the community's hospital and affiliated Staff. We chose this area because of the existence of a good base of general practitioners and general surgeons and a dearth of internists. We chose a community hospital administration committed to health care and willing to provide us with the means for performing the diagnostic tests outlined in Table 1. It was important for us to have a large referral center (Maine Medical Center) within a reasonable distance from our hospital. Finally, a reliable and efficient laboratory and radiology department are of the essence. We were fortunate to find a hospital with both of these services.

Which features of our own practice, as we have set it up, have we found most helpful in the delivery of good care? There is no question that basing our practice on the problem-oriented method has been invaluable, especially when the need arises to obtain up-to-date information accurately and quickly when we cross-cover each other. The use of the problem-oriented record and associated disease file allows us

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TABLE 1

TYPES AND NUMBERS OF PROCEDURES DONE IN THE FIRST EIGHTEEN MONTHS OF PRACTICE	
Bone Marrow Aspiration and Biopsy	18
Bronchoscopy	19
Elective cardioversion	18
Laryngoscopy	4
Liver Biopsy	7
Pacemaker Implantation — Temporary, Transvenous	12
Panendoscopy	47
Swan-Ganz Catheterization	25
Treadmill Submaximal Stress Testing	172

to audit patient care by reviewing disease entities monthly and thereby add to our own continuing education. Secondly, the close proximity of our office to the hospital is essential, especially since we care for many acutely ill patients. Thirdly, it has been a hard and fast rule of our practice that every new patient entering the practice undergo a complete history and physical examination. This allows us to know well the patients for whom we care.

What may an internist expect to do and see in rural private practice? We have all had the experi-

ence of vacationing in some bucolic country setting, wishing on the one hand that we could live there forever, and dreading on the other hand the endless parade of sore throats and runny noses which we would have to endure through such a decision. This fear has not been realized. The spectrum of disease that we have seen has been wide and varied. The common and challenging problems of internal medicine such as arteriosclerotic heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, cancer, cirrhosis and arrhythmias have been seen in abundance.

During residency training it is easy to develop the feeling that fascinating and unusual diseases are seen only in the university center. We, however, have been impressed and, frankly, awed by the number of unusual cases that we have encountered in our past eighteen months. Table 2 represents a listing of some of these unusual cases. With the ability to do the procedures outlined in Table 1 and the facilities provided by the hospital to do so, we have found that approximately ninety-five percent of the medical problems we see primarily or in con-

TABLE 2

"UNUSUAL" CASES SEEN	
Allergy	Heart
Syndrome of nasal polyps, asthma and aspirin	I.H.S.S.
Arrhythmias	Dissecting aneurysm
Recurrent supraventricular tachycardia treated with fixed rate ventricular pacing	Congenital aortic stenosis — severe
Arthritis	Acute ruptured papillary muscle secondary to myocardial infarction
Gonococcal sepsis with arthritis	Acute myocardial infarction in a thirty-two-year-old woman
Psoriatic arthritis	Suppurative pericarditis in a patient with chronic lymphatic leukemia
Arthritis of sarcoidosis	Hematology
Bone	Myeloproliferative disorders
Paget's disease	Multiple myeloma
Osteomyelitis	Acute myelocytic leukemia
Collagen Vascular Diseases	Reticulum cell sarcoma
Temporal arteritis	Infectious
Systemic Lupus Erythematosus with cerebritis	Overwhelming influenza pneumonia
Raynaud's disease	SBE
Mixed collagen vascular disorder	Primary syphilis
Congenital	Liver
Congenital rubella syndrome with aortic stenosis — ? secondary to bicuspid aortic valve	Chronic active hepatitis
Turner's syndrome with Hashimoto's thyroiditis	Secondary biliary cirrhosis
Dermatology	Neurologic
Psoriasis	Guillain-Barré syndrome complicated by aortic stenosis and insufficiency
Pemphigus	Charcot-Marie-Tooth
Ehlers-Danlos syndrome	Primary and secondary brain tumors
Endocrine	Oncology
Addison's disease	Mesothelioma
Severe hypothyroidism with precoma	Thymoma
Myxedema with severe coronary artery disease	Carcinoma of the ureter
G.I.	Embryonal cell carcinoma of the testes
Ascending cholangitis with secondary biliary cirrhosis	Renal cell carcinoma
Gallstone ileus in a lady with nephrotic syndrome and poly- cythemia vera	Carcinoma of the gallbladder
Hemorrhagic pancreatitis	Oat cell carcinoma with inappropriate ADH syndrome
	Sarcoma — rhabdomyosarcoma liposarcoma leiomyosarcoma
	Respiratory
	Rheumatoid lung disease
	Sarcoidosis

sultation are diagnosed and managed in the small forty-two bed community hospital in which we work. This kind of comprehensive care has tremendous implications for both patient and doctor and is, after all, what internists are trained to do.

The final issue which we would like to address is that of the possible intellectual sacrifice inherent in leaving an urban area and academic setting. There is no question that we miss daily contact with medical students, house staff, and full-time academicians. The stimulus for continuing education which they provide is unquestionable. In a rural practice the stimuli must come from other sources. One such source is inherent in our daily contact with each other. In addition, we give many medical staff lectures, are responsible for tumor conferences and for coronary care nurse-education programs. Also, we have become involved in the community emergency medical technician training courses. While the audience is different, the willingness to learn is no less than that found at a medical center. The entire experience fulfills our need to continue teaching. For our own continuing medical education, programs such as those sponsored by the American College of Physicians are of paramount importance to us. However, the greatest stimulus to learn, we have found, lies in the experience of diagnosing and managing the many patients who have many diseases of many systems. One finds oneself not reading about brucellosis but rather about Mrs. Smith, and the

impetus to learn is profound. By necessity, our office library is up-to-date with current journals, textbooks and tapes.

In summary, we have found that in our rural setting we are able to practice what we were trained to do. With the admission of more complex and critically-ill patients to our hospital, the goals of the hospital have changed to that of a diagnostic as well as a therapeutic medical center. Patients who before had to be transported great distances for specialized care are now being cared for in the community. We have found the problem-oriented record to be a vital part of our private practice and of our continuing medical education. Interesting and unusual diseases are as abundant, if not more so, here in Norway, Maine, than they were during our training program. The intellectual and academic experience is a different one qualitatively but does certainly not differ in quantity. We can say without reservation after our initial eighteen months of practice that being a general internist in rural America is a most rewarding and challenging experience. We feel strongly that the general internist is still a vital force in America's health care system. He can function as both a primary care physician and a consultant when he utilizes the training he has received in an area where he is needed.

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# The Renin-Angiotensin System in Hypertension

MICHAEL A. LACOMBE, M.D.\*

The renin-angiotensin system plays an important role in at least some forms of hypertension. However, considerable controversy exists with regard to the number of patients who are hypertensive because of a derangement in this system, and with regard to determining when derangement of the system has occurred. With development of a radioimmunoassay for plasma renin activity (PRA), theoretically one might predict when abnormalities in the renin-angiotensin system are producing hypertension in the patient. It is the purpose of this paper to review the current status of knowledge of the renin-angiotensin system, the various methods proposed for evaluating the renin system in the hypertensive patient and the "typing" of hypertensive patients and their consequent treatment.

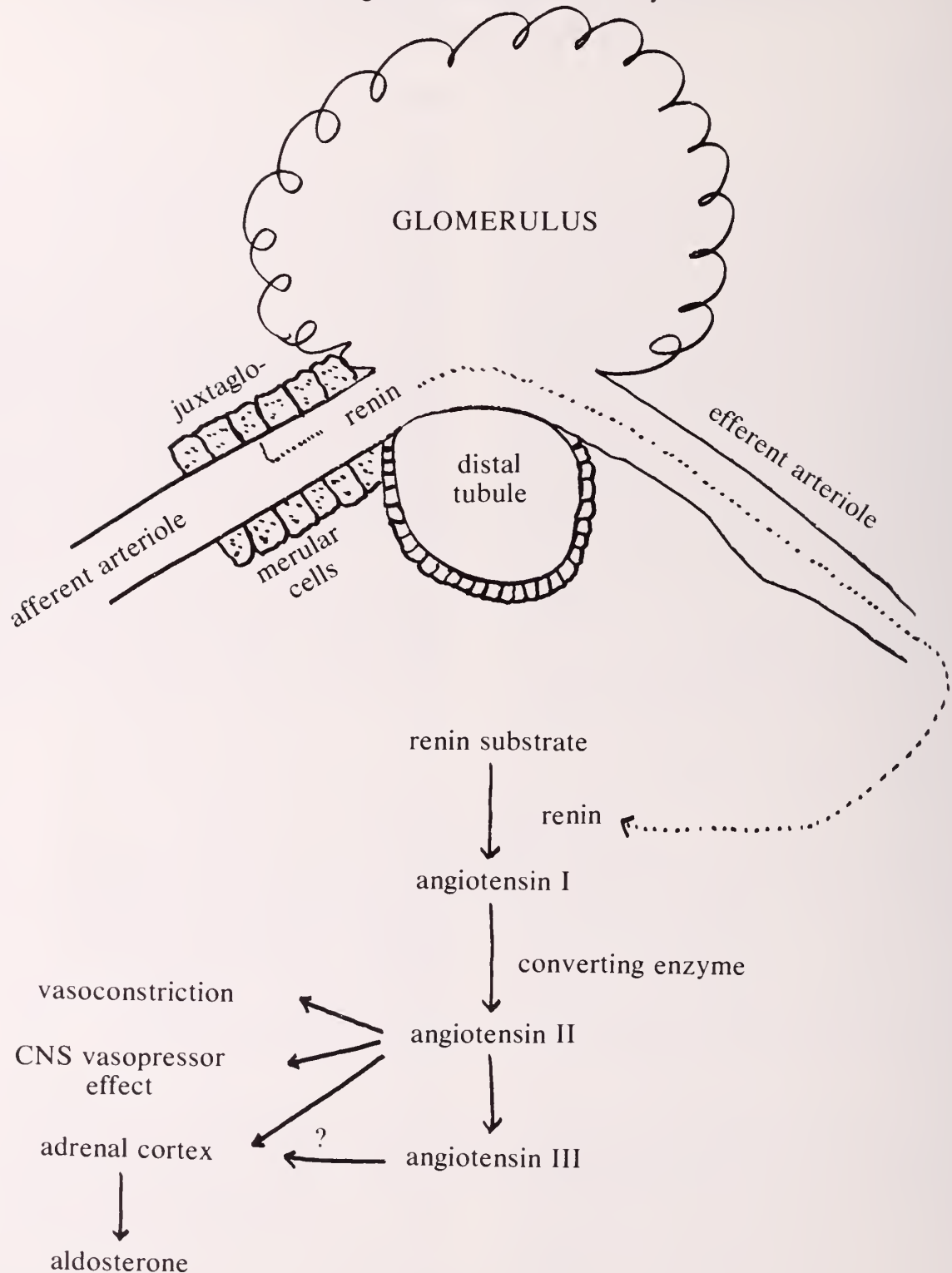
There have been several recent excellent reviews of the physiology of the renin-angiotensin system.<sup>1-5</sup> The biochemistry and physiology of the renin axis will therefore be reviewed only briefly here (see Figure 1). In response to changes in perfusion pressure mediated through catecholamines and in response to changes in sodium concentration in the distal tubule, the juxtaglomerular cells of the afferent arteriole degranulate releasing renin into the renal circulation. This enzyme, renin, cleaves a circulating glycoprotein, renin, substrate, producing angiotensin I, a decapeptide. Converting enzyme located in lung tissue acts upon angiotensin I during its passage through the pulmonary circulation, producing the octapeptide angiotensin II. This peptide, a potent vasopressor, acts directly upon arteriolar smooth muscle to produce vasoconstriction. In addition, it produces a vasopressor effect through its indirect action on the central nervous system.<sup>2</sup> Lastly, angiotensin II acts upon the adrenal cortex to produce the mineralocorticoid aldosterone which in turn results in sodium conservation, volume retention and further increased perfusion of the afferent arteriole. (There is some evidence that aldosterone release may also be effected through a metabolite of angiotensin II, so-called angiotensin III.) Several feedback loops serve to keep this system in balance. An understanding of these feedback loops is key to an understanding of the classification of hypertension according to circulating plasma renin activity. Vasoconstriction and sodium retention, the latter mediated through aldosterone, will increase perfusion pressure in the afferent arteriole

and thus presumably decrease the need for and the secretion of renin. There is evidence also that angiotensin II has itself a direct negative feedback effect on the juxtaglomerular cells.<sup>2</sup> Therefore, if an anatomic defect, i.e., renal artery stenosis, decreases perfusion pressure of the afferent arteriole, one would expect increased circulating levels of renin and, hence, of angiotensin II. Conversely, should a primary hypersecretion of aldosterone or an aldosterone-like mineralocorticoid exist, one would expect, through feedback inhibition, lower than normal plasma renin activity.

The most exciting development in the study of hypertension in recent years has been the grouping of hypertensive patients into classes of low-, normal-, and high-plasma renin activity. Theoretically at least, those with extremely low PRA should have hypertension secondary to hormonal causes, i.e., excessive mineralocorticoid activity and consequent volume overload. At the other end of the spectrum, those with extremely high PRA should have their hypertension secondary to decreased perfusion pressure (due to coarctation, renal artery stenosis, etc.) and would therefore have hypertension on the basis of a vasoconstrictive effect rather than on the basis of volume overload. (Those with normal PRA are still classified as "essential hypertension;" the term "essential" used to shield our ignorance about this group of patients.) It is at this point that one becomes embroiled in one of the major controversies in this field. Plasma renin activity, even in the face of demonstrable and severe pathology, is markedly influenced by a variety of environmental factors. Diet, posture, medication, and even the degree of existing hypertension, all effect the level of PRA. There are, in short, a number of variables which have to be controlled for, and there exists at present no standard accepted method of measuring plasma renin activity, although many techniques are reported in the literature. Two reasonably reliable methods for measuring PRA have been proposed by Laragh and by Wallach. Laragh and associates express PRA in relationship to 24-hour urine sodium excretion and have published nomograms of renin activity versus urinary sodium for normal subjects.<sup>6</sup> Using this method, normal and hypertensive subjects, regardless of sodium intake, demonstrated consistent PRA values when corrected for 24-hour urine sodium excretion. An objection to this method has been the difficulty in obtaining, and the reliability of, the 24-hour urine collection. Hence, a "stimulated renin"

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Figure 1  
Renin-Angiotensin-Aldosterone System



technique has been developed whereby the patient is given an oral diuretic which, presumably through changes in sodium concentration in the macula densa, stimulates plasma renin which is measured sometime after the diuretic challenge. Using 60 mg

of furosemide orally with PRA measured five hours later in the upright posture, Wallach and associates proposed this stimulated renin technique as a screening test for hypertension.<sup>7</sup> In screening forty hypertensive patients in this manner, four patients

with high PRA were identified and ultimately demonstrated to have renovascular hypertension. Two patients with low PRA proved to have primary aldosteronism. There are, however, blemishes on this very attractive, scientific picture of hypertension. For example, in the high renin group, significant populations of patients with renal vascular hypertension and *normal* plasma renin activity have been described.<sup>8</sup> In addition, as alluded to above, the degree of hypertension seems to affect plasma renin activity; raising the blood pressure in a normal individual will decrease his PRA. That is to say, with increased perfusion pressure, the negative feedback loop works, and patients with severe "vasoconstrictive-type" hypertension may have falsely low PRA (false-negative). Although hypertensive patients seem to lose this capacity to diminish PRA with increasing blood pressure, this variable has to be corrected for.<sup>9</sup> Finally, extremely high PRA may be found unassociated with hypertension. The most vivid example of this phenomenon is the patient with Bartter's syndrome of hypokalemic alkalosis, juxtaglomerular cell hyperplasia, elevated PRA and serum aldosterone and normal blood pressure. We have one such patient in our practice who would, in terms of the high-PRA class, constitute a false-positive.

Controversy exists over whether or not the existence of high-plasma renin activity might be an added risk factor in the hypertensive population. That is to say, is renin itself vasculotoxic? In a controversial paper, Brunner and associates reported an increased frequency of heart attacks and strokes in patients with normal or high renin activity.<sup>6</sup> In this study, 219 patients with essential hypertension were evaluated for frequency of heart attack and stroke. None of the 59 low renin patients suffered these complications and appeared to be protected despite similar hypertension. In contrast, patients with normal or high renin had an 11 and 14% frequency respectively of heart attacks and strokes. Although other studies have supported this thesis, namely, that renin is an added risk factor in hypertensive disease,<sup>10,11</sup> the weight of evidence at the present time seems to be to the contrary.<sup>12-15</sup> Those studies which dispute Brunner's findings have pointed out errors in selection of the patient population and differences in the degree of hypertension and postulate that since those patients with low PRA are more easily controlled, that may be the reason why they have fewer complications from their hypertension. Whereas, initially the thrust of Brunner's argument was that one should be more aggressive in treating high-renin hypertension, the evidence now would suggest that all hypertensives should be vigorously treated regardless of renin profile.

This controversy leads us to a discussion of the treatment of hypertension per se, apropos of plasma renin activity. The aim of therapy is to control the hypertension primarily and not to lower plasma

renin activity. In addition, one need not avoid drugs which tend to increase plasma renin activity under the assumption that such an increase in plasma renin will prove vasculotoxic. Yet, if Laragh's thesis is correct, that all hypertension is divided into pressor- or volume-related disease, then it would make sense to use a renin-lowering drug for the pressor type of patient and a diuretic for volume-related hypertension. Considerable research has been directed toward this question. It has been shown that propranolol inhibits the release of renin from the juxtaglomerular cells rather than interfering with its synthesis and is thus a very effective and available renin-lowering drug.<sup>16</sup> Buehler, et al, showed that in hypertensive patients with increased PRA, propranolol alone consistently controlled the hypertension, producing a fall in blood pressure directly related to the fall in plasma renin activity.<sup>17</sup> Although renin profiling for the treatment of hypertension had been advocated by Laragh's group, more recent studies argue strongly for diuretic therapy as the initial mode of treatment in mild essential hypertension, regardless of PRA.<sup>18</sup> On this point I choose to compromise. I advocate treating all mild-hypertensive patients initially with a diuretic alone. The more severely hypertensive patient should be renin-profiled and, if a high-PRA is found, should be treated with increasing doses of propranolol. Finally, with regard to the treatment of hypertension, one would hope for some help from renin profiling with the task of recommending surgical "cure." Ideally, the hyperreninemic patient could have his renal artery stenosis promptly repaired, and the hyporeninemic patient, his aldosteronoma removed. In reality, however, those patients at the ends of the spectrum of renin profile are not always helped by surgery. Many patients with extremely low or absent plasma renin activity and with micronodular hyperplasia of the adrenal cortex may not be "cured" by surgery. There is some evidence, though, that spironolactone in high dosages (300 mg per day) can be used to predict surgical success, since those patients who fail to respond to this drug would not benefit from surgery either.<sup>3</sup> Similarly, an angiotensin antagonist is now being used to screen hyperreninemic patients for surgery.<sup>8,19,20</sup> Saralasin, a weak agonist of angiotensin II, competitively inhibits the peripheral action of angiotensin II on smooth muscle. Saralasin has been infused in hyperreninemic patients to identify those patients whose increased PRA is vital to perpetuation of their hypertension and has also been used in unselected hypertensive populations to determine which of these patients belong to the surgically curable hyperreninemic population. This exciting new development in the diagnosis of hypertension may well completely skirt the issue of renin profiling since it may be assumed that those patients who respond to the drug with a drop in blood pressure have hypertension secondary to increased PRA (and hence increased angiotensin II) and would benefit from

surgery. One problem with giving saralasin to an unselected hypertensive population is that, since the drug is a weak agonist, it may produce a paradoxical elevation in blood pressure in patients with low renin activity.<sup>20</sup> Saralasin may also be of benefit in determining which hypertensive patients on birth control pills would benefit from stopping the oral contraceptive therapy. In some such patients, oral contraceptive preparations elevate PRA; these people would be expected to have a fall in blood pressure during a saralasin infusion. Other hypertensive women may not be hypertensive because of the pills nor because of increased PRA and would have no response to the saralasin.<sup>8</sup> For the patient with moderate or severe hypertension, I believe subclassification by PRA profile to be of benefit. Although admittedly patients with very high or very low PRA may not necessarily be helped by surgery, renin profiling will nevertheless indicate which patients require further study. One should study in depth the difficult-to-control hypertensive patient, even though his PRA may be normal, since a normal PRA does not necessarily mean that a secondary cause for the hypertension is not present. When it has been decided that PRA determination may be of some benefit in the management of the hypertensive patient, the patient should abstain from all medication for one month prior to PRA determination. A 24-hour urine sodium should be collected together with a plasma renin activity determination and the results compared with the nomograms of Brunner, et al.<sup>6</sup> Immediately following the urine collection and baseline PRA level, a furosemide stimulation test can be done, giving the patient 60 mg of furosemide with a second PRA level drawn five hours later during upright posture. The results of the stimulation test can be compared to the nomogram of Wallach, et al.<sup>7</sup>

In summary, determination of plasma renin activity is of some benefit. It seems not to be of value in determining which patients will be more likely to have a "vasculotoxic" complication of hypertension, i.e., stroke and heart attack. In addition, it seems to be of no value in predicting response of the hypertensive patient to therapy. There is no rationale for avoiding drugs in the treatment of hypertension which increase plasma renin activity. For the mild "essential" hypertensive patient diure-

tic therapy should be the initial mode of treatment. Finally, when a patient with extremely high or extremely low plasma renin activity is found, thought must be given to the use of inhibitors of the renin-angiotensin-aldosterone system for predicting surgical cure.

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# Femoral-Posterior Tibial Modified Umbilical Vein Bypass Graft

SABRY E. MASON, M.D.\* and PETER E. GIUSTRA, M.D.\*\*

After two unsuccessful femoral popliteal bypass grafts, using a saphenous vein in the first operation and a Dacron® prosthesis in the second, the pre-gangrenous left leg of a 79-year-old woman was spared amputation by a femoral posterior tibial modified umbilical vein bypass graft. This is believed to be the first use in Maine of this recently developed biograft and its persistent patency five months after surgery in an otherwise not salvageable limb seems worthy of this case report.

## CASE REPORT

A 79-year-old female with mild diabetes mellitus was admitted to the Camden Community Hospital in May 1977, for above knee amputation of the left leg. She was complaining of constant rest pain in the left leg and had gangrenous ulcers of the toes. One toe was amputated one year previously for ischemic gangrene. The patient had a long history of arteriosclerotic peripheral vascular disease; and on different occasions over the last three years, she underwent bilateral carotid endarterectomies and bilateral femoral popliteal bypasses using autogenous saphenous vein grafts. Claudication of the left leg and gangrene of the second left toe recurred one year after surgery due to occlusion of the saphenous vein graft and subsequent progression of her peripheral vascular occlusive disease. A repeat femoral arteriogram in January 1977, revealed occlusion of the vein graft and a very poor run-off from a patent distal popliteal artery. A second femoral popliteal bypass was performed using an 8 mm. knitted Dacron prosthesis, and the second toe was amputated. This graft occluded a short time postoperatively, and the patient developed constant rest pain and ischemic gangrenous ulcers in the remainder of her toes.

Examination on the present admission revealed a strong femoral pulse, absent popliteal and pedal pulses, and the patient was admitted for above knee amputation. A repeat selective femoral arteriogram at the Penobscot Bay Medical Center revealed complete occlusion of the superficial femoral, popliteal and the trifurcation arteries (Fig. 1). Only the distal portion of the posterior tibial artery at the ankle was patent (Fig. 2). A femoral posterior tibial bypass was performed using a modified human umbilical vein graft. The posterior tibial artery was exposed by an 8 cm. long incision, 1 cm. behind and parallel to the posterior edge of the tibia, to confirm the artery's patency and suitability for anastomosis. The flexor digitorum longus muscle was separated from the soleus muscle exposing the neurovascular bundle. A 5 cm. segment of the artery was separated from the venae comitantes and from the posterior tibial nerve. The common femoral artery was then exposed by a longitudinal incision in the groin. The proximal portion of the artery was found suitable for anastomosis.

Two umbilical veins, each 36 cm. long and 8 mm. in diameter, were sutured together end to end using 6-0 Tevdek® material. The anastomosis was a simple over and over stitch approximating intima to intima. A long tunnel was made between the incision above the ankle and that in the groin. The tunnel ran along the neurovascular bundle in the leg, through the popliteal space and



Fig. 1. Selective left femoral arteriogram, after two unsuccessful femoral popliteal saphenous vein bypass grafts, shows complete occlusion of the popliteal and trifurcation arteries.

behind the medial head of the gastrocnemius and then along Hunter's canal beneath the satorius muscle. A small counter incision was made at the level of the knee to facilitate the construction of the tunnel. The proximal anastomosis was performed first after trimming the end of the umbilical vein obliquely permitting an end to side common femoral artery anastomosis using 5-0 Tevdek material. The biograft was made to lie in the tunnel without torsion or kinks. The lower end was trimmed for end to side anastomosis to the posterior tibial artery which was about 2-3 mm. in diameter. This anastomosis was 1 inch long, using 6-0 Tevdek material with interrupted sutures at the toe and heel of the incision and a running continuous suture at the sides to avoid a purse string effect on the suture line. No vascular clamps were

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Fig. 2. Delayed radiograph of the ankle during a selective femoral arteriogram demonstrates a patent distal posterior tibial artery at the ankle (arrows).

applied to either the posterior tibial artery or the umbilical vein graft.

Following completion of the anastomosis, an operative arteriogram was performed by injecting 50 cc. of Renografin-60® into the upper end of the umbilical vein using an 18 gauge needle. A film centered over the lower leg demonstrated patency of the graft and excellent vascularization of the foot (Fig. 3). Postoperatively, the patient was given small doses of Coumadin® and Heparin®, and was immobilized for one week with a Zimmerman's knee immobilizer.

The patient left the hospital two weeks later with a pulsating umbilical vein graft and strong pedal and posterior tibial pulses. Five months later the patient still had a strong peripheral pulse, and all the gangrenous ulcers in her toes had healed. Her claudication had completely subsided.

#### DISCUSSION

A limb with the angiographic findings of completely occluded popliteal and trifurcation arteries (Fig. 1) and only a single visible patent artery at the ankle (Fig. 2) might be salvaged with a long saphenous vein bypass graft. In a patient with no autogenous bypass tissue available, however, (both saphenous veins had been used in previous surgery and cephalic veins would not be of adequate length and diameter) and the previously documented likelihood that a bovine heterograft or Dacron prosthesis of such a length across a joint would occlude, amputation would be the commonly performed surgical procedure.

As a desperation measure to save the leg of our patient, a femoral posterior tibial modified umbilical vein bypass graft was performed. The graft was

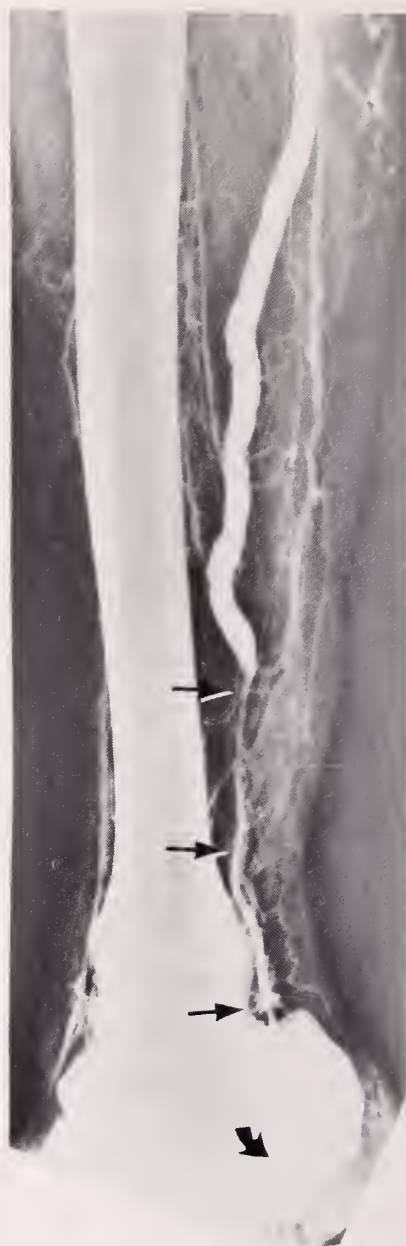


Fig. 3. Operative femoral arteriogram demonstrates a patent femoral posterior tibial modified umbilical vein bypass graft and patent distal posterior tibial artery (arrows). There is excellent vascularization of the foot (curved arrow).

obtained directly from Herbert Dardik, M.D. of Englewood Hospital, New Jersey, the pioneer in the development and use of the umbilical vein biograft.<sup>1,2</sup>

Human umbilical vein is tanned with glutaraldehyde as the untreated vein acts as a xenograft and is rejected. During the tanning process, glass rods may be inserted in the vein to change its diameter to an appropriate size. The tanned vein is surrounded by a polyester fiber mesh for increased stability, maintenance of uniformity, and prevention of aneurysm formation. The biograft, so modified, then becomes an ideal material for long bypass procedure. It is "impervious, valveless, unbranched,

uniform in diameter, and readily available."<sup>1,2</sup> Its success in arterial bypass in the lower limb has been recorded in both animals and humans.<sup>1,2</sup>

We found the umbilical vein graft a delight with which to work. It has a tough wall and holds sutures well. One of the difficulties encountered in using a saphenous vein graft is that the vein must be reversed because of valves, and its narrow end sutured to the common femoral artery. The umbilical vein is superior to the saphenous vein in this respect. It has a uniform diameter along its entire length and is free of valves. The use of an umbilical vein graft eliminates surgical time and trauma entailed in removal of autogenous saphenous vein. The umbilical vein withstands kinking across joints. In the fetus it is often knotted without interrupting the foetal blood supply. Despite its favorable characteristics, the umbilical vein should be handled carefully and placed in the tunnel without undue tension, torsion, or kinks. Interrupted sutures of 5-0

and 6-0 Tevdek material, well lubricated with bone wax, are used. The vein should be thoroughly washed of preservatives and chemicals with heparinized Saline solution.

To date, the modified umbilical vein is available only from Dr. Dardik's laboratory in New Jersey. The vein is prepared in various lengths or two veins can be sutured together to provide a long graft. Dr. Dardik continues research in the various uses and application of this excellent biograft, and his results to date are very promising. The modified umbilical vein may well replace artificial prostheses and autogenous vein grafts in peripheral vascular bypass surgery.

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### Warning — From Section on Ophthalmology of the Maine Medical Association

Statement of the Committee on Conservation of Vision on the use of topical corticosteroids for the eye.

In its report to the Maine Medical Association this year, the Committee expressed renewed concern over the use of topical ophthalmic corticosteroids (usually in the form of an antibiotic-corticosteroid preparation) without slit-lamp monitoring for eye inflammation. The concern is that such corticosteroids activate any herpes simplex in the cornea to cause extension of the corneal scarring produced by the virus, and it has been the experience of ophthalmologists to see such cases where the corneal scarring has gone on to blindness.

It is true that conjunctivitis responds more quickly to such preparation, but because most cases of conjunctivitis are self-limited anyway, they do not warrant the added risk from a corticosteroid, and any bacterial conjunctivitis is quickly controlled by an appropriate topical antibiotic alone.

In the practice of the ophthalmologist, if a corticosteroid has to be used for an eye inflammation, he follows by slit-lamp examination during the course of the use of the topical corticosteroid so that any herpes virus keratitis can be detected in its early stage when it can be controlled (though even this may be difficult).

Emergency Room physicians and the preceptors of family practice residents are not always aware of the risk of using topical corticosteroids without slit-lamp monitoring so that they have been prescribing them and teaching others to do so; and physicians who have been practicing for a long while, using antibiotic-corticosteroids topically as a routine for conjunctivitis, may say that they have never had such a complication of herpetic keratitis. In such case they have been very lucky, or the herpetic keratitis that has occurred has come under the care of an ophthalmologist without the physician who first attended the case becoming aware of the complication.

Therefore, the Committee asks that the Maine Medical Association publish this communication.

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# An Ounce of Prevention

FRANK W. KIBBE, M.D.

There are few individuals with greater susceptibility to sepsis than the elderly who live in nursing homes and extended care facilities. Indeed, if there is a group more liable to infection, it is probably the elderly receiving cancer chemotherapy whose immune systems are fatigued with age and then made ineffective by chemotherapeutic agents.

Is it in error to emphasize that prevention of infection in these situations is more to be desired than cure or to ask what steps are being taken on behalf of those least well equipped to stand the impact of such disease?

An example will show that far from enough is being done to set proper standards, carry out and evaluate effective procedures, or monitor this susceptible segment in an effort to prevent increasing morbidity by infections. Over a period of two weeks in our laboratory, we cultured four pseudomonas infections from four different individuals in a single nursing home. Each patient had his own physician different from the others, so no one was conscious of the overall problem. An alert bacteriology technician pointed out the problem to me, but had cultures gone to various laboratories or had various technicians covered bacteriology in one laboratory who would have been the wiser? Who is there to screen such situations? By government edict, small-pox, rabies, etc. are reportable, but out of such a background should not gram-negative organisms, staphylococci and candida be equally reportable? I ask this only because the *Journal of the American Hospital Association* has continued to take a stand against monitoring where on many occasions such organisms might be found and cleaned up before any human infection results. Lack of proper controls for this group extends well beyond the problem of infection of course. To illustrate: Four senior patients in a nursing home were studied over a period of about three months for work completely unconnected with anemias (i.e. preoperative checks, acute infections, etc.) Each patient was from a different nursing home and each had a hemoglobin of four (4) grams or less. None of these people had had any sort of blood check for over a year.

In the State of Maine's "Regulations Governing the Licensing, etc." of Skilled Nursing Facilities, I find on page 72 the rules about housekeeping services concerned with cleanliness, safety, etc. In addition, notes are set forth to guide an infection control committee with designations for "written policies & procedures." One wonders about such control committees, when and how they meet and if such a committee is not under the wing of a general hospital staff how any control measures can be monitored. A colleague of mine who had to do some

suturing in such a facility recently suggested to the charge person that she might be more effective in establishing sterile conditions by putting on Voodoo masks and dancing about the bed than by carrying out present cleaning procedures. Incidentally, I see nowhere in the State of Maine regulations anything about methods of cleaning or the necessity of having a steam sterilizer. It is well to have the "written" procedures, but who monitors the solutions, the rooms and the people?

As to new facilities applying for licensure, we are in the same bind as with new hospitals. An infection control committee is an "after the fact" procedure. In Maine only<sup>1</sup> Dr. George Wood and his Tuberculosis control program seem to realize the necessity for the pre-work screening of individuals and the necessity for therapy before allowing workers or patients into any facility. In his letter concerning working personnel and inmates, he outlines completely the methods of coverage, both testing and treatment, to afford protection to others. However, I have seen nothing in state bulletins about screening of personnel for parasites or staphylococcus infections to eliminate the presence of carrier people, nor for the culturing of rooms or instruments to find errors in technique.

If extended care rooms and certain nursing homes come under the aegis of a medical center, are these centers willing and able to monitor their poor relations? Is the infection control committee at all conscious of the early spring and late fall fly problem in older homes as well as occasionally in the most modern of buildings with suspended ceilings? Vectors need not be humans alone, but even to that end have we any laws or even rules concerning the study of the hands of attendants in homes? We scrub and then glove and gown in our operating rooms, but once a patient is discharged from the acute care area, does anyone bother to scrub in connection with dressing wounds and would occasional colony counts emphasize the importance of cleanliness? Transfer of organisms in such a milieu is more than possible, it is probable. Who is reviewing the course of an institution where single minor infections may predispose to the start of a pseudomonas or monilia invasion? Is some commercial laboratory responsible? Where does the state or public health enter the picture? On a local level is any one physician aware of the threat of infection by patients under another physician's care?

In a film produced by the University of Texas Southwestern Medical School on gram negative bacillary pneumonia, there is considerable emphasis on routine surveillance of inhalation equipment including bacterial counts. Accurate record

keeping is just as essential to the decontamination program as the counts themselves. To quote: "All respiratory therapy devices should be checked periodically for contamination." The film does go on to say that the small volume medication nebulizers do *not* provide a significant source of respiratory infection, but constant checks are certainly necessary.

What then of hand washing in nursing home facilities? Adequate washing is the greatest safeguard against cross infection and cross contamination, but if washing stands are not immediately available to all patients the procedure may be skipped. By regulation there must be at least one lavatory for each six residents so some distance to the sink becomes evident. Monitoring hands with colony counts helps to pinpoint poor scrubbing techniques as well as emphasize to physicians and nurses the importance of adequate cleansing. One<sup>2</sup> study showed a drop from 27% to 13% positive cultures where concentrated hand washing was the rule.

Further to the surveillance and screening as a major defense, I wonder if the laundry or patient rooms in these premises are ever checked by bacterial rodac plates or fallout cultures. It is well to state that no dry sweeping or dusting is to be used, but unless records of bacterial counts are kept, no tool for enforcement of policy is available. To quote from *Control of Infection in Hospitals*, "the only effective housekeeping program is one that is continually checked and evaluated." Even if nursing homes have some sort of infection control group, unless they have in hand bacterial reports on hands, rooms, laundry and disinfectants they can exercise no sort of control and cannot know of the sword of Damocles over their residents. Because one cannot expect complete isolation techniques in these surroundings, patients who pose a threat to others must of necessity, when the threat becomes known, be moved to an acute care hospital.

<sup>3</sup>According to Dr. G. Collison of the New Zealand Bureau of Health, cancer therapy patients in Auckland, New Zealand, are cared for in a single unit of the hospital where reverse isolation can be practiced and this cannot be the case in the general nursing home situation. Most of such patients do stay at home but come to a separate outpatient unit, so no contact is made with general hospital or ambulatory patients.

Present day teaching dictates early discharge, so the tendency is to unload the acute hospital case as rapidly as possible in order to: (a) lessen expense and (b) reduce the patient's exposure to in-hospital infection. By doing this are we losing the knowledge that might aid in control of post-operative or hospital induced infection? Patients go home or to a nursing facility, and the original hospital has lost contact and thus certain knowledge of any post-hospital complication unless it is severe enough to require rehospitalization. Do physicians' offices or nursing

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homes report into the original hospital's infection control group? Are cultures automatically taken under these extra-hospital circumstances?

Again in New Zealand I learned through Dr. Ruthven Lang that patients discharged from the Auckland Hospital are followed via an extramural hospital system, not too different from our home health services, but in Auckland all discharged patients enter this system. Thus, all post discharge infections data is entered into the Auckland Hospital system even though the patient does not necessarily return to become an inpatient. Dr. Lang, who is in charge of the Infection Control program in Auckland, is trying to elicit the cooperation of all departments: surgical, medical, pediatrics, etc. to evaluate the entire scope of the nosocomial infection problem. He is looking to the area of pre-operative patients who have infections that might pose a threat to operating rooms, recovery areas or even the general hospital. He has, in addition, considered the value of area and personnel monitoring with an eye to turning up potentially dangerous areas or people. Most careful consideration is being given to bacterial counts in the nursery, operating rooms and surgical supply sectors. Returns here may be small but prophylactic medicine in the hospital environs can be as rewarding as culturing the city water or milk supplies. In the larger 500-600 bed hospitals of New Zealand, there is normally a microbiologist on the committee to aid in infection control and usually it is he who first is conscious of an in-hospital or iatrogenic infection and is most cognizant of cross-contamination. The checking of solutions used in the hospital is also in his hands as well as the power to limit specific antibiotics in general hospital use.

With tight government supervision of medicine, New Zealand has thus made some progress in dealing with nosocomial infection. Nevertheless, New Zealand public health is faced with many of the same situations found in this country. Present control of communicable diseases in New Zealand, community or hospital, hinges on reports to the public health system, but it applies only to the reportable diseases as smallpox, diphtheria, tuberculosis and the like. Thus, no cross-infections with gram-negative bacilli, fungi, or staphylococci ever surfaces. Even the post-fact action of a public health reportable disease may be delayed. Again, via a discussion with Dr. G. Collison, I learned of a diphtheria case the notice of which did not reach her office until some two weeks after the fact because of some questions arising concerning the strain of the organism. In our close quartered nursing homes such luxury of time might well be fatal.

Even in this socialistic medical atmosphere no prophylactic work is done in new hospitals or other new medical care buildings. There is no type of continuous monitoring of anything beyond the acute care facility. Even this may be sparse, being dictated entirely by the infection control committee of that individual hospital, such as the committee

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that I met with chaired by Dr. Lang. It is within the right of the Public Health Officer to order transfer of a patient with a communicable disease out of a nursing home into the isolation sector of the acute general hospital. It could also be within his or her province to do the same with wound infections, if reports concerning such infections reached him and he felt that such infections were a threat to a community. In practice such culture reports never reach the public health level according to Dr. Collison.

In Chapter 15 of Maine's "Regulations governing licensing..." I note that "no resident with a communicable disease shall be kept in any facility unless a satisfactory plan for a regimen of care has been approved by the Department." This statement certainly recognizes the problem at hand, but avoids the issue of the non-reportable infectious agents that can peruse such an institution. Thus, no tight control can possibly exist in our "extra-hospital" patient care units unless they are directly allied or under the wing of a medical center. Such a center could have knowledge of internal infection threats, could control antibiotic use, could monitor fly-infested areas and could screen personnel.

Again in Chapter 21 of the Maine "Regulations governing licensing..." much is said in detail concerning physical features as doors, corridors, ramps and maintenance with great emphasis on fire protection. This is extremely laudable for protection of the aged, and of course a fire in such a facility becomes public knowledge, particularly when deaths ensue. Deaths in such institutions from cross-infections are scarcely within the interest of the public domain and are thus hardly newsworthy. The rules dictated about screening of garbage areas as well as all outside windows should serve to minimize the fly vectors but human vigilance is still of primary importance in defeating this pest.

Where does the responsibility for the infirm el-

derly lie? One opens Pandora's Box when one invades the nursing home community that serves such a necessary function. To quote George Will, we may be extending the "fallacy of the false alternative," for indeed neglect of local infection control need not result in a multiplicity of cross-infections. Before we effect some change here should we await repeated in-home infections and the possibility of legal action which often speaks much louder than medical admonition?

Is all this philosophical folderol? Rather than end on a completely negative attitude, may we suggest a policy to abort the almost inevitable nosocomial infections in the nursing home environs? If every physician working or consulting in these circumstances could have at his behest an agency which would not only take reports about poor technique and inadequate sterility but which, in addition, could act on such reports to improve conditions, then I think we would have a weapon to block cross-infections among our very susceptible nursing home residents. It should also be within the power of such an agency to monitor areas and solutions in such homes and require rectification of discrepancies via the threat of "loss of license."

#### ACKNOWLEDGMENTS

I wish to thank Eleanor Hutchinson and Patty Jones for their great help in the area of bacterial identification.

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R.F.D. 2, Lincolnville, Maine 04849

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## Fall Meeting of the M.M.A. House of Delegates

Saturday, December 10, 1977

Mid-Maine Medical Center (Thayer Unit), Waterville, Maine

12:30 P.M. — Registration; 1:00 P.M. — Lunch; 2:00 P.M. — Meeting

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10:00 A.M. — Meeting of the Executive Committee

# The Medical Examiner System — Role Of The Physician

HENRY F. RYAN, M.D.\*

## ABSTRACT

**For years the national trend has been to replace lay coroners with physician-medical examiners. The following article discusses the reasons for this shift and presents the fundamentals of what is required of medical examiners in the State of Maine.**

## INTRODUCTION

As the science and art of determining the cause of death became more complex due to the increasing sophistication of the medical profession, government realized that the responsibilities of the coroner could best be handled by those skilled in the art and science of medicine. The profession itself recognized the importance of this function and boards were established in forensic pathology — a subspecialty in pathology.

Largely because of the frequent but by no means universal experience that elected and appointed laymen and physicians who became coroners through a highly political processes, did not exhibit high standards of competence the position of coroner gradually fell into disrepute. Less political processes for appointment were instituted, the position was restricted to physicians, and the title "coroner" was dropped in favor of the title "medical examiner" in many places. The term "medical examiner" remains largely misunderstood, with the public associating it with insurance physicals or physician licensing. Many of the best forensic pathologists in the country still retain the title "coroner" — a title that is immediately understood by virtually everyone and which retains a connotation of legal powers beyond mere diagnosis of the cause of death. The title is unimportant — a more serious question is whether or not the position should be reserved for physicians in view of the fact that many parts of the country have a shortage of physicians and even where no shortages exist it can be argued that physicians can better utilize their time in direct patient care. Before pursuing this further, let us define the role and purpose of a medical examiner.

## RESPONSIBILITIES OF A CORONER-MEDICAL EXAMINER

A medical examiner is charged with certifying the cause, circumstances, place, time and date of death and identity of the deceased. To those ends he employs the technique of observation, history taking

from relatives and witnesses, reviewing of past medical records, examination of the body, autopsy consultation, laboratory follow up studies and the services of investigative agencies, usually law enforcement departments.

The cause of death is usually determined from past and terminal medical history and if necessary autopsy and laboratory studies. The place, time and date of death are determined by observation, eyewitness accounts, examination of the scene and body, and investigative information from other agencies.

The identity of the deceased is determined in most cases by relatives or friends but may require comparison of fingerprints and dental records, and past medical history, especially past surgery, with the body in question.

The circumstances — homicide, accident, suicide can sometimes be determined by examination of the body but generally for traumatic deaths the circumstances are determined from observations at the scene and further investigation. For example: A person falling to his death at the bottom of a cliff could have stumbled — accident; have jumped — suicide; or have been pushed — homicide. Examination of the body would yield identical findings in all three cases. Only the investigation would reveal the true circumstances. If the person had suffered a heart attack and for that reason had fallen, the autopsy might provide enough information to properly establish the cause and circumstances of death. Occasionally the investigation cannot resolve the issue and some coroners retain the power to subpoena witnesses and take testimony under oath to establish the circumstances of death. This function has largely been transferred to grand juries with the resultant loss of the quasi-judicial role of the coroner. For this reason there is less necessity for coroners to have a strong legal background.

The coroner investigates and certifies death to serve the needs of the community in two areas: deaths not due to natural causes and deaths due to natural causes when no one else is available to certify them.

First, all deaths due to trauma or poisoning are considered not due to natural causes regardless of whether the poisoning is acute or chronic, whether the trauma is man made or an act of God, whether the person dies immediately or is under a doctor's care for some time, even years, or whether the death is the direct result of traumatic process such as hemorrhage or by late, natural complications of the

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trauma such as pneumonia. This is often misunderstood and it is common to have deaths certified by attending physicians if the victim survives in the hospital for some time. Regardless of the length of time under a doctor's care, regardless of how long the person survives after the trauma, and regardless of what the terminal pathology causing death had been if the death is ultimately ascribable to the trauma the case should be reported to and certified by a medical examiner. This is true for three reasons: It is the law. It allows for orderly centralization of records in all such cases. It permits a full co-ordinated investigation of the incident including police investigation and an autopsy, if necessary, even over the objections of the next of kin.

The second broad category includes apparent natural deaths with no evidence of trauma or suspicion of foul play which cannot be certified by a physician because the deceased had no regular physician; is young, way below the age where sudden death might be expected and his physician has never treated him for a serious illness (including S.I.D.S.); comes to his death some distance from his home such as on a vacation trip or when the deceased's physician is himself on a long vacation out of the area. Difficulties arise when the physician is merely on a day off locally, is employed by a clinic as a radio-therapy-radiologist, nephrologist, or oncologist, or has only cared for the patient for a short time perhaps an hour or so in the hospital. None of the above justify making the case a medical examiner's case. So long as there is good reason to believe that the person died of natural causes and a reasonable clinical judgement can be made from history, signs, symptoms, and statistics as to the cause the private physician should certify the death. He can establish such a cause of death within minutes of seeing the patient for the first time such as in myocardial infarcts and can certify the cause weeks after he last saw the patient such as in known severe heart disease or terminal cancer. Days off, hospital based practice, and long distances do not justify placing the burden of certifying the death upon a physician who volunteers for medical examiner work as he too may be hospital based, on his day off or a long distance from the death. The physician who has been treating the patient is in a better position to certify the death and give consolation to the family and has an obligation not to abandon his patient for this last call. Inability to be absolutely sure what the cause of death is is no excuse — medical examiners cannot be absolutely sure in most cases and have less information than the regular attending. It is particularly irksome and demoralizing for a medical examiner to travel many miles in the wee hours of the morning during a snowstorm to certify a quiet natural death in the home of a chronically ill elderly person when the private physician lives just down the street. Nursing home deaths should never be medical examiner cases except when there is evidence of trauma or

foul play since nursing home residents all have attending physicians and are in nursing homes because of advanced age and/or ill health. Partially, but by no means entirely, because police responding to such deaths by reflex call a medical examiner our system in Maine handles 500-600 more cases than we should. This is an unfair burden on the individual medical examiners whose purpose is not to provide convenience services to other physicians and it is also poor public relations for our profession if its members refuse to help the family of the deceased in their time of need.

#### WHY PHYSICIAN-CORONERS?

From the preceding it should already be clear that only physicians can properly evaluate past medical history and symptoms and examine the body so as to arrive at a reasonable cause of death but in addition to this there are several other reasons why physicians should be medical examiners:

- 1) They add a prospective to the consideration of the case that law enforcement officers do not have.

- 2) They have sufficient background to adequately explain and defend their medical determination.

- 3) They can interact with the community in its time of need thus aiding the image of medicine in general as a profession serving the public needs at the same time as they extend their personal contacts with the community and its officials.

- 4) They help to stem the tide of recent years which has caused an even tighter withdrawal of physicians into the nucleus of patient care away from the very important periphery of general health services. More and more physicians have withdrawn or been forced out of important positions on the periphery of medical care such as regional planning, hospital administration and public health into the compact nucleus of direct doctor-patient services. As a result the profession has been charged with shirking its responsibilities and has lost much influence in the community. This loss of image and influence is already seriously affecting day-to-day practice.

- 5) Should the medical profession withdraw from coroner responsibilities the function must be assumed by others outside the profession and it is inevitable that eventually the coroner system will become to some extent a reviewing agency of the adequacy of medical care and this reviewing agency will be entirely outside the profession without the knowledge or perspective to properly evaluate the cases. I do not believe that even the physician based coroner system is prepared to handle complex questions of malpractice which should properly be evaluated in another forum.

#### WHAT IT MEANS TO BE A MEDICAL EXAMINER IN MAINE

All medical examiners are physicians, licensed as Doctors of Osteopathy or Medicine, and residents of the State. They are appointed to indefinite terms

of office by the Chief Medical Examiner and have Statewide jurisdiction though, for practical purposes, they exercise their authority in the area of their residence and practice. They serve for a fee of \$30 per case. The majority handle fewer than one case per month. They may be called by the police, hospital, family, or undertaker. Upon receiving such a call they first determine if it is a medical examiner's case or should be referred to the family physician or other practitioner. If they accept the case, they then decide whether they must proceed to the scene of death or view the body later. If there is any doubt that the victim is dead, the persons at the scene should procure the help of the nearest available medical services or transport the victim to a medical facility and not wait for a medical examiner to determine the fact of death. Whether or not they view the body at the scene or later at the funeral parlor or hospital medical examiners must thoroughly examine the body making written notes of their findings and obtain, either by personal investigation or through some other agency, the circumstances and reduce these to a written report on forms provided by the State. They then complete the physicians portion of the death certificate which is left with the body. The medical examiner's report is sent with an invoice for their services to the Chief Medical Examiner's Office. Should an autopsy or other studies be necessary they make appropriate arrangements. These services, when completed, are billed directly to the State.

Since, with the exception of the Chief Medical Examiner, all medical examiners in Maine are part time, emergency needs of their practice may preclude their accepting a particular medical examiner case and the inquiring party may be referred to another medical examiner. Of course, the greater the number of medical examiners the less work for any one individual. A few physicians, because of ill health or contractual arrangements such as E.R. staff, have "limited service" status whereby their services are requested only as a last resort or within the confines of their place of practice. For the most

part no formal regional scheduling is attempted and medical examiners serve as available. Since all major criminal cases are referred to the Chief Medical Examiner or autopsied by another pathologist, medical examiners are very rarely called into court. If they are, they are compensated for their appearance.

Many physicians are reluctant to take on medical examiner work as they are unfamiliar with that type of practice. This fear can be dispelled by the facts that there is a detailed reference manual provided by the State to every medical examiner and that consultation is always available either from the Chief Medical Examiner or a particularly experienced person in the area. Other problems such as transportation in foul weather can be worked out with the assistance of the police or sheriff's office and legal advice is readily available from the Attorney General's Office or the District Attorneys. A law has been passed, to take effect this fall, that protects medical examiners from personal liability arising from their medical examiner duties though experience has shown this to be an almost non-existent problem and that when it has occurred the State has represented the medical examiner and assumed full responsibility.

#### CONCLUSION

This article has emphasized the need for physicians as medical examiners and outlined the overall functions of medical examiner offices and individual medical examiners. Mention has been made of some of the areas where non-medical examiner physicians can help the system by their co-operation. Anyone interested in becoming a medical examiner can do so simply by writing or calling the Chief Medical Examiner's Office, State Office Building, Augusta, Maine 04333 — 289-2993. Because of the round the clock, 365 day nature of the work and the large area served, there is no part of the State where additional services are not needed. It is important that this essentially medical responsibility be adequately met by the profession through continuous recruitment of interested physicians as medical examiners.



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## Intravenous Fluid Therapy

DAVID H. LAWSON, M.D., F.R.C.P. and DAVID A. HENRY, M.B., M.R.C.P.

Intravenous fluids are among the most commonly prescribed drugs in hospitalized patients in the United States.<sup>1</sup> In 1974, an estimated 100 million large volume parenteral solutions were administered in the United States.<sup>2</sup> Up to 54% of medical inpatients in one U.S. hospital participating in the Boston Collaborative Drug Surveillance Program received intravenous fluids, as compared with 7% in an Israeli hospital.<sup>3</sup> Moreover, when a comparison was made between two Scottish hospitals that participated in this study, considerable differences in the frequency of intravenous fluid use were apparent, even in comparable groups of patients.<sup>3</sup> Thus, major differences exist in the use of this type of therapy — both between and within countries.

This review summarizes the indications for the use of large volume parenteral solutions and describes the types of fluids administered and their potential hazards.

### INDICATIONS FOR INTRAVENOUS THERAPY

Parenteral fluids are indicated primarily to replace fluids previously lost from the body or to maintain homeostasis in those who are unable to do so unaided.

#### *Replacement Therapy*

Sudden major loss of body fluids requires rapid replacement which can be achieved only by the intravenous route. The choice of fluid is guided by the clinical problem. Whole blood is the appropriate treatment for hemorrhage and may also be used in the emergency management of massive fluid loss from burns. When blood is not available, other colloid solutions such as reconstituted plasma, plasma protein fractions or dextran solutions can be used, although the latter may interfere with subsequent blood grouping and may have a detrimental effect on blood coagulation.<sup>4</sup>

Normal saline is frequently used to replace fluids lost during prolonged vomiting, diarrhea, intestinal obstruction, ileus, the recovery phase of acute renal

failure, or in Addison's disease. In these disorders, the addition of potassium is necessary. The clinical use of potassium supplements is reviewed elsewhere.<sup>5,6</sup>

Dextrose 5% in water is indicated to replace depleted extracellular water, as in diabetes insipidus, following excessive sweating, or during prolonged coma. This solution may, however, be inappropriate under certain circumstances, such as non-ketotic diabetic coma, when hypotonic saline is the fluid of choice.<sup>7</sup>

#### *Maintenance Therapy*

In a number of clinical situations, oral fluid intake is precluded for a limited period; examples are intestinal ileus, peritonitis, after abdominal surgery, or during severe systemic infection or prolonged coma. Under these circumstances, maintenance intravenous therapy must supply the entire fluid and electrolyte requirements of the patient. Assuming that any deficiencies have already been corrected, the fluid requirement of the average adult is around 25 to 40 ml/kg body weight per day. The average requirement for sodium is approximately 135 to 170 mEq per day, and for potassium, approximately 80 to 100 mEq per day. In practice, the average adult is given two liters of fluid in 24 hours, using 5% dextrose and normal saline with added potassium supplements. Provided renal function is intact, normal homeostatic mechanisms will ensure adequate salt and water balance over a wide range of intake, thus relieving the physician of the need for obsessional attempts at providing the exact physiological requirements for each patient. Unfortunately, such mechanisms are less effective in conserving potassium homeostasis, so greater care is required with this ion than with either sodium or water intake.

#### *Emergency Venous Access*

Establishment of an intravenous line is often considered essential in the management of many clinical situations, even when disordered fluid balance is not a prominent feature. This attitude undoubtedly results from a fear that access to a vein to inject essential drugs will otherwise prove difficult in the event of a sudden deterioration in the patient's condition. The need for establishing an infusion when a patient experiences serious arrhythmias following myocardial infarction is evident, but the provision of parenteral fluids for every individual admitted

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with chest pain or a questionable gastrointestinal bleed is unjustified. The potential benefits of routine intravenous therapy should be balanced against the potential hazards. Where doubt remains, the use of an indwelling cannula containing a heparin solution ("heparin lock") should be sufficient for most needs.

## HAZARDS OF INTRAVENOUS THERAPY

### *Thrombophlebitis*

Thrombophlebitis is primarily a physicochemical phenomenon and is uncommon within 24 hours of catheterization of a peripheral vein.<sup>8</sup> After this period, the incidence increases in relation to the length of time the catheter is left *in situ*.<sup>9</sup> This complication occurs more frequently with dextrose infusions, possibly due to their extremely low pH.<sup>10-12</sup> Attempts to reduce the incidence of thrombophlebitis by using buffered dextrose solutions or by adding heparin or hydrocortisone to the infusion fluids have been only partially successful.<sup>8,13-15</sup> Despite the high prevalence of post-catheterization thrombophlebitis, pulmonary embolization appears to be uncommon unless the thrombus extends to involve the deep venous system — a rare complication usually arising from catheterization of peripheral veins in the lower limb.

### *Infection*

Infusion-associated sepsis is potentially serious, since the organisms have direct access to the circulation. Many potential sources of infection arise during the manufacture and administration of parenteral fluids. Recent incidents in the United States and Great Britain involving large-scale contamination of parenteral fluids during manufacture resulted in patients developing nosocomial septicemia — a potentially fatal condition.<sup>16,17</sup>

The subject of infection control in intravenous therapy has been extensively reviewed by Maki and co-workers.<sup>9</sup> They highlighted four major areas in which sepsis could complicate the use of parenteral fluids.

1. *Catheter insertion.* Skin flora are frequent contaminants of intravenous catheters, and adequate sterilization of the skin of both operator and patient prior to venipuncture is an essential although frequently neglected procedure.<sup>11</sup> Solutions containing chlorhexidine, alcohol, and iodine are effective antiseptics<sup>18-21</sup> although the latter may produce allergic reactions or cutaneous burns, particularly when used in high concentrations.<sup>22</sup> Shaving of hair from venepuncture sites is not essential and may increase the risk of introducing organisms by alterations of skin flora.<sup>23</sup>

2. *Type of catheter.* The relation of long-life plastic catheters to infusion-related sepsis is controversial. The frequency with which organisms can be isolated from catheters varies widely, from 4 to 45% in different series.<sup>11,24</sup> Sepsis is particularly common with infusions sited in the lower ex-

trémities,<sup>25</sup> where long-life catheters are frequently used. Moreover, the proportion of positive cultures from catheters increases with time in all sites.<sup>24</sup> Although no clear-cut relationship has been demonstrated between bacterial isolation from catheters and infusion-related septicemia, both these complications are much more common when the catheter is left in place for more than 48 hours.<sup>9</sup> The higher prevalence of bacterial isolation from plastic as opposed to steel catheters has led to the belief that plastic catheters are associated with greater risk of infection.<sup>9</sup> One possible explanation for this finding is the smaller bore of metal cannulae, which results in less trauma to the venous endothelium.<sup>26</sup> However, it is more likely that fluid extravasation from the vessel occurs at an earlier stage with the metal device, thereby necessitating a more frequent change of cannula.<sup>9</sup> This also explains the current popularity of plastic catheters.

3. *Thrombophlebitis.* Although most investigators agree that physical trauma or chemical irritation are the prime causes of phlebitis, prospective studies have shown a possible association between the occurrence of thrombophlebitis and infusion-related septicemia. In particular, during the much publicized "Abbott incident," a higher rate of thrombophlebitis was found among infected patients than among those who did not develop sepsis.<sup>9</sup>

4. *Contaminated infusion fluids.* Bacterial contamination of infusion fluids can occur during manufacture or as a result of any medical or nursing procedure which disturbs the integrity of the container or administration set. Failure of commercial sterilization techniques is probably rare, but when it occurs the results can be devastating.<sup>27</sup> A study conducted by the Center for Disease Control in Atlanta revealed 378 cases of septicemia in 25 hospitals after the nationwide use of a batch of infected infusion fluid.<sup>16</sup> The organisms isolated in this and other similar outbreaks were of the *Enterobacter* group. These bacteria are rare pathogens in man that have an unusual ability to survive the normally bacteriocidal environment of strongly acidic dextrose solutions.<sup>28,29</sup> Their isolation in blood cultures indicates the possibility of a contaminated infusion.<sup>27</sup>

Infection of infusion fluids can also occur following trauma to the container; tiny cracks in glass bottles or micropunctures of the newer plastic bags provide portals of entry for invading organisms.<sup>9</sup> Contamination can result from injection of drugs into the infusion fluid or administration set, and airborne invasion may result from the use of airways for ventilation of the older rigid containers.<sup>30</sup>

Discovery of contamination usually occurs after the recognition of an adverse event in a patient, since visible changes in appearance of solutions occurs only with very heavy contamination.<sup>27</sup> When contamination is suspected, the infusion should be discontinued immediately with removal of both administration set and catheter.

### *Volume Overload*

When excessive volumes of isotonic intravenous fluids are administered to a healthy individual, the increase in venous return to the heart stimulates cardiac output and can increase urine volume to a maximum of approximately 16 ml/min. With an increased solute load after infusion of hypertonic saline, mannitol, or urea, an osmotic diuresis may occur with even higher urine flow rates. If an increase in cardiac output or glomerular filtration cannot be sustained because of cardiac or renal disease, a rise in pulmonary and, later, systemic venous pressure will ensue with accumulation of fluid in these areas. Since defective handling of sodium accompanies most cardiac and many renal diseases, serious volume overload occurs most frequently when such patients receive infusions of saline and, in particular, hypertonic solutions. Early signs of fluid retention should be watched for whenever a patient with known cardiac or renal disease receives intravenous fluids.

### *Air Embolism*

Venous air embolism is usually considered the most dramatic complication of parenteral fluid therapy. In fact, it is probably necessary to inject air at a rate of 70 to 100 ml/sec to a total of over 200 ml to produce sudden death as the result of acute cor pulmonale.<sup>31</sup>

Infusing fluid into a peripheral vein in a dependent limb using a nonpressurized system, it is highly unlikely that such a large volume of air could be introduced, and the risk is lessened even further by the use of flexible nonventilated containers. The safety of modern infusion techniques is illustrated by a review of over 116,000 blood transfusions in which no recorded cases of fatal air embolism occurred.<sup>32</sup>

Central venous catheters, however, are more hazardous. Air embolism has been reported as a fatal hazard of percutaneous puncture of the subclavian vein.<sup>33,34</sup> The risks are greater when the patient is hypovolemic and the catheter is inserted in the sitting or semi-recumbent position.<sup>31</sup> The resulting negative pressure in a large vessel can introduce a substantial volume of air quickly, either during the catheterization procedure or if the infusion set subsequently becomes detached from the hub of the catheter by accident.<sup>33,35</sup>

### *Particulate Matter*

The possible circulatory effects of the injection of particulate matter are seldom considered and generally receive much less attention than some of the more obvious hazards of parenteral fluid therapy. To be visible to the naked eye, particles in suspension must be greater than 50 microns in diameter.<sup>36</sup> Thus, visible clarity of the solution will not guarantee its safety, since invisible particles as small as 12 microns in diameter will not pass through the smallest capillaries and will be trapped in the pulmonary vascular bed.<sup>37</sup> The particulate content of commer-

cial infusion fluids is fairly high, although improved manufacturing techniques have reduced this form of contamination.<sup>38</sup> The most common foreign substance is rubber, in the form of fragments dislodged from bungs during autoclaving.<sup>39</sup> The increasing use of disposable plastic containers should reduce this source of contamination. However, many other different types of particles have been found in intravenous solutions, varying from metal fragments to fibers, molds, and even insects. The opening of large numbers of glass ampuls in the preparation of an injection carries the hazard of introducing glass fragments into the body.<sup>40-42</sup>

Little is known about the effects of particulate matter on the body. It is likely the lungs bear the main burden of any injury. Cellulose fibers are particularly irritating, stimulating the formation of granulomata.<sup>40</sup> Pulmonary hypertension and respiratory failure have been noted among recipients of long-term intravenous therapy, and it may be that pulmonary edema may sometimes be due to particulate damage in the lungs rather than volume overload.<sup>43</sup>

### *Chemical Contamination*

The advent of disposable nonvented flexible fluid containers has undoubtedly reduced the risk of contamination of intravenous solutions by bacteria and particulate matter. The long-term effects of this change, however, are not known. Interest has recently centered around the possible toxicity of chemicals used in the plasticizing of polyvinyl chloride (PVC). These substances, in particular di-2-ethylhexalpthalate (DEHP), can leech out of the walls of the container and accumulate in the tissues of patients receiving blood transfusions or treatment with parenteral fluids.<sup>44</sup> Although the significance of this finding remains to be established, the possible toxic effects of the plasticizers and stabilizers utilized in the production of PVC will require further investigation, particularly in patients receiving long-term parenteral fluid therapy or multiple blood transfusions.

### **CHOICE OF PARENTERAL FLUIDS**

More than 70 different basic large volume solutions are marketed in the United States. This is surprising, since the great majority of clinical situations can be managed with 5% dextrose and normal saline solutions, with the addition of potassium chloride as required. The use of mixed solutions, particularly those claiming to contain balanced quantities of electrolytes, should be discouraged since they may foster a false sense of security in the clinician who is often unaware both of the exact components contained in the solution and of the needs of the particular patient.

### *Saline Solutions*

*Normal saline.* 0.9% saline contains 154 mEq of sodium and of chloride per liter. It has, therefore, a

slightly higher osmolality and sodium content than normal plasma. This is not a major disadvantage as its main use is the replacement of deficiencies of extracellular fluid volume. The use of normal saline should be avoided when the patient has a high serum sodium concentration—a situation that requires the use of solutions which replace extracellular water alone. Although hyponatremia and hyperchloremia can be induced by overtreatment with normal saline, volume overload with resulting pulmonary edema is a more common result.

**Half-strength saline.** 0.45% saline contains 77 mEq of sodium and of chloride per liter. It is hypo-osmolar with respect to plasma and can be used to replace deficiencies of extracellular water. It is most commonly used in the treatment of hyperosmolar diabetes mellitus where the use of dextrose is inadvisable and there is a need to provide large amounts of fluid without an excess of sodium ions.

**Hypertonic saline.** Solutions of sodium chloride with strengths ranging from 1.8 to 5.0% are available for the treatment of severe sodium depletion, but they should be used with the greatest caution. Hyponatremia frequently indicates water overload with resulting hemodilution, and the total body sodium is often normal or even high.<sup>45</sup> The use of hypertonic saline solutions in this situation may induce or aggravate pre-existing cardiac failure with fatal consequences. If genuine sodium deficiency appears to be present and the serum sodium concentration is dangerously low (less than 120 mEq/l), hypertonic saline may be infused slowly; if necessary, a short-acting diuretic may be used to prevent fluid overload. This situation arises infrequently.

#### *Dextrose Solution*

**Dextrose 5%.** Water can be infused most conveniently in the form of 5% dextrose. This is a safe solution whose osmolality (277 mosm/l) is slightly less than that of plasma. The glucose content is quickly metabolized in normal individuals, although the nutrient value is slight (190 calories per liter). Dextrose solutions are acidic and tend to induce thrombophlebitis.<sup>10</sup> The low pH (3.5 to 5.0) should also be considered when large volumes have to be infused quickly, especially in patients with pre-existing acid-base disturbances.

**Higher strength dextrose solutions.** Dextrose solutions with strengths varying from 10 to 50% are available, the more concentrated being valuable for the immediate correction of hypoglycemia. Dextrose 50% solution has a high viscosity and, therefore, must be injected under pressure. Ten to twenty percent solutions provide 380 to 760 calories per liter and can be used to manage conditions such as hepatic or renal failure where a high calorie intake in the form of carbohydrate is indicated. These high-concentration dextrose solutions are intensely irritating to peripheral veins and, therefore, should be infused through long catheters into the superior or inferior vena cava.

#### *Fructose (Levulose)*

Since fructose is rapidly metabolized independently of insulin, it is popular as a calorie source in the treatment of conditions such as diabetes mellitus and liver failure. It has also been used successfully in the treatment of acute alcohol intoxication.<sup>46</sup> Unfortunately, during fructose infusion the rate of lactate formation exceeds its clearance, with the consequent accumulation of lactate in the blood. This tendency to develop lactic acidosis is particularly marked in liver failure,<sup>47</sup> diabetes mellitus, and in the presence of ethanol,<sup>48</sup> and it may preclude the use of fructose in the very conditions in which it should be of greatest value.

#### *Alkaline Solutions*

**Sodium bicarbonate.** Sodium bicarbonate is the most convenient solution for the correction of metabolic acidosis. It is usually prepared locally in the hospital pharmacy. A 1.43% solution provides 170 mEq of sodium and bicarbonate ions per liter; it is the safest strength for routine use but is not widely available. Unfortunately, rapid correction of acidosis with this solution requires injection of a large volume of fluid; this has led to the use of an 8.4% solution in emergencies. This solution contains 100 mEq of sodium bicarbonate per 100 ml, thus simplifying the calculation of requirements. During the chaos of cardiac arrest, patients often receive larger doses than intended, with consequent sodium overload and metabolic alkalosis. This complication may seriously compromise the likelihood of successful resuscitation.<sup>49,50</sup> The high sodium content of bicarbonate solutions is a drawback when they are used in renal failure, and rapid correction of acidosis in this condition engenders risk of acute tetany if intravenous calcium supplements are not provided.

**Tromethamine (THAM).** Tromethamine is an organic buffer, usually available as a 0.3 M solution adjusted to a pH of approximately 8.6 through the addition of acetic acid. It is hypertonic but free of sodium ions. Its use has been advocated in the treatment of most types of acidosis; because of its unique ability to neutralize carbonic acid it was originally considered valuable in the management of respiratory failure. Experience with tromethamine in this situation has revealed that correction of acidosis is associated with further respiratory depression; modern techniques of assisted ventilation have obviated the need for buffering solutions. Because it is eliminated entirely by the kidney, tromethamine is contraindicated in uremia. A further hazard is hypoglycemia, which can result from infusion of large amounts of tromethamine. There is currently no evidence to support the use of tromethamine in preference to bicarbonate solutions in the management of acidosis.<sup>51</sup>

**Sodium lactate.** When lactate is infused into normal individuals, it is metabolized to bicarbonate. Unfortunately, this conversion is markedly delayed

in the presence of tissue anoxia, and excessive lactate accumulation may occur with worsening acidosis.<sup>48</sup> A number of proprietary mixed electrolyte solutions contain lactate as a bicarbonate precursor, and they are best avoided in situations where this conversion may be impaired.

*Sodium acetate.* The problems associated with the use of sodium lactate do not occur with sodium acetate, since it is converted to bicarbonate in the citric acid cycle even under anaerobic conditions. It offers no real advantage over bicarbonate solution except that it is cheaper and can be stored for longer periods in hot climates.<sup>52</sup>

#### AGENTS USED TO TREAT ALKALOSIS

Metabolic alkalosis is almost always accompanied by deficiency of chloride and potassium ions, of which correction using normal saline with added potassium chloride will often reverse the acid-base disturbance. When more rapid correction of alkalosis is necessary, administration of ammonium chloride can provide a positive balance of hydrogen ions.<sup>53</sup> However, its intravenous use is accompanied by the danger of ammonia accumulation with resulting encephalopathy. Because of this hazard, some workers have advocated the infusion of hydrochloric acid in the treatment of severe alkalosis.<sup>54</sup> Hydrochloric acid must be given through a central venous catheter, since extravasation from peripheral veins may result in severe tissue necrosis. A further hazard is hemolysis — this has occurred after the infusion of 0.3 N hydrochloric acid. The use of hydrochloric acid should be confined to solutions with a concentration of 0.15 N or less.<sup>55</sup>

#### INTRAVENOUS POTASSIUM THERAPY

Potassium chloride is available as a 15% (by weight) solution containing 2 mEq/ml. This solution must never be injected in the undiluted form as cardiac arrest will result. It is customary to add potassium chloride to infusion bottles in a concentration of 40 mEq/l, and infusion rates generally should not exceed 10 mEq per hour.<sup>6</sup> In clinical situations characterized by rapid changes in the plasma potassium concentration, such as the diuretic phase of renal failure or during a forced alkaline diuresis, potassium can be infused at rates exceeding 20 mEq per hour, but this should only be attempted in the presence of biochemical and electrocardiographic monitoring. Fatal hyperkalemia has occurred after the addition of potassium chloride to modern flexible containers in the upright position because of pooling of the added potassium at the bottom of the container.<sup>56,57</sup> Adequate mixing of these solutions must be ensured prior to the commencement of an infusion.

#### CALCIUM SALTS

Calcium is given intravenously only when rapid correction of hypocalcemia is necessary, or when the patient is unable to maintain normal calcium

balance by the oral route. Various solutions are available for injection, but in practice a 10% solution of calcium hydrochloride (1.3 mEq/ml) or calcium gluconate (0.45 mEq/ml) will meet most requirements.

Calcium salts are highly irritating, and necrosis with subsequent sloughing of tissue has followed extravasation of solutions containing calcium chloride.<sup>58</sup> In this respect calcium gluconate is safe and is preferable.<sup>59</sup> Injections of calcium should be given slowly as transient hypercalcemia may induce acute cardiac arrhythmias. Calcium salts are incompatible with a number of drugs in solutions,<sup>59</sup> and if mixed with sodium bicarbonate precipitation of insoluble calcium carbonate will result.<sup>60</sup>

#### MAGNESIUM SALTS

Magnesium is the principal intracellular divalent cation and is essential to the functional integrity of almost every organ and tissue in the body. Despite the identification of magnesium deficiency in a wide range of disease states, including diabetes mellitus, hepatic cirrhosis, intestinal malabsorption, and patients on long-term diuretic therapy,<sup>61-64</sup> controversy still exists as to the benefits of magnesium supplementation in these conditions.

The approximate human daily requirement for magnesium is 20 to 40 mEq, but the normal kidney effectively conserves this cation under conditions of reduced intake.

Intravenous magnesium replacement may be necessary in severe deficiency states. Magnesium sulfate as a 10% solution (0.81 mEq/ml) is preferred. The main hazard associated with its use is hypermagnesemia characterized by neuromuscular blockade and respiratory depression. Calcium and magnesium ions have mutually opposing and competitive actions on the body; thus intravenous calcium gluconate will partially reverse the effects of acute magnesium intoxication.

#### MIXED SOLUTIONS

A large variety of mixed electrolyte solutions are available. The number of products and the diversity of their content is both confusing and potentially hazardous.

*Premixed potassium solutions.* In order to circumvent the problems associated with the addition of potassium chloride to flexible fluid containers (see section on potassium therapy), several manufacturers now provide premixed solutions of potassium chloride in dextrose or saline. These solutions are safe so long as the user is aware of the exact potassium content; this should be clearly marked on the container.

*Dextrose/saline mixtures.* A solution containing 0.45% saline and 2.5 to 3% dextrose has the theoretical advantage of providing a fluid which is approximately iso-osmolar with plasma while containing only a modest quantity of sodium and chloride ions. This solution is not widely available, and the more

commonly used mixture of 0.9% saline and 5% dextrose is undesirable in view of its high osmolarity.

**Multiple electrolyte solutions.** A large number of products claim to contain "balanced" mixtures of essential electrolytes. Some of these solutions represent attempts to reduce the excess of sodium and chloride ions present in normal saline by substituting cations such as potassium, calcium, and magnesium or anions such as lactate or acetate. The resulting mixtures vary widely in their constitution and bear little relationship to the actual electrolyte requirements of most patients. As stated earlier, the great majority of clinical situations can be managed with judicious use of 0.9% saline and 5% dextrose with the addition of other electrolytes as determined by the needs of the individual patient. In practice, the only cation which should be routinely considered is potassium.

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# Maine Blue Cross and Blue Shield News

## SUBSCRIBER CONTRACTS UPDATED

Occasionally we have to update the Blue Cross and Blue Shield subscriber contracts to bring them up-to-date with benefit and policy changes as well as new State laws. The changes listed here are now in subscriber contracts, and the new contracts are being distributed.

### BLUE CROSS COVERAGE

*Maternity Care* — maternity benefits are available to any female member (married or single, including dependent daughters) if the pregnancy begins after the effective date of coverage.

*Nursery Care* — routine nursery care is covered regardless of the mother's qualification for maternity care.

*Inpatient Diagnostic* — benefits provided for diagnostic services to hospital inpatients were expanded to include full coverage for diagnostic services.

*Outpatient Coverage* — full coverage is provided for diagnostic outpatient laboratory and pathology services in the hospital outpatient area when related to a specific illness or injury or a definitive set of symptoms.

*Cosmetic Surgery* — coverage for a cosmetic or congenital defect existing prior to the member's effective date of coverage is not covered unless there is an impairment of function. This exclusion does not apply to a newborn child who becomes properly enrolled under a contract.

*Medical Necessity Review* — Assuming the patient has benefit days in the hospital left, and has not been formally discharged by his or her physician, Blue Cross coverage for inpatient hospital care will end 72 hours from the date on which the patient receives notification from the Hospital Utilization Review Committee that further hospitalization is not medically necessary.

### BLUE SHIELD COVERAGE

*Physician* — the term physician has been replaced with the word "professional" to cover various types of doctors.

*Psychologists* — psychologists are listed as professionals eligible for reimbursement when their services are rendered to an inpatient in a General Hospital.

*Maternity Care* — as with Blue Cross coverage, the 270 day waiting period has been replaced with a provision whereby coverage is provided if the pregnancy begins after the Effective Date of coverage. Again, this applies to married and single female members and dependent daughters.

*Newborn Care* — coverage is provided for newborn circumcisions resulting from birth abnormalities or congenital defects.

A complete list of benefits and allowances can be found in your revised Blue Shield physician's manual which was printed in July. If for some reason you do not have a copy, write to the Provider and Professional Relations Department, Blue Cross and Blue Shield of Maine, 110 Free Street, Portland, Maine 04101.



DAVID E. SMITH  
COMMISSIONER

## Maine Department of Human Services

# Investigation of a Large Scale Tuberculosis Outbreak

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ADA C. KNAUFF, R.N. and STANLEY ROSENBLATT, M.D.\*\*

In mid-December 1976, a Maine physician reported a case of tuberculosis in a 20-year-old boy. The patient had been coughing for months or even perhaps up to two years. In the six months before diagnosis, the patient had run a low grade, intermittent fever and experienced a weight loss of twenty pounds. Tuberculin skin test was positive, chest x-ray revealed bilateral upper lobe infiltrates and sputum cultures grew *M. tuberculosis*. The patient had been identified as a contact of an elderly man with active TB ten months earlier, but had refused skin testing at that time. In retrospect, it is difficult to determine whether the young man or the elderly one had been ill first.

It was soon discovered that a number of aspects of this case were unique. The patient lived and worked in a fairly small, isolated and socially "inbred" Maine community (1970 Population 2246). He worked as an egg gatherer at an egg farm which employed some 700 people, many who lived locally. A trailer park directly on company grounds provided housing for some employees. It was not uncommon for an employee to work with the same people who were his neighbors and that he also saw on a social basis. Our TB patient was such a person: his entire life was inextricably linked with the lives of other employees at the plant. He worked with them, ate with them, saw them socially in the evenings, dated at least one female employee or met them at the small neighborhood store. He also lived with many of them; he was a natural drifter and during the year preceding diagnosis of his illness, he lived with at least five different households. Finally, he loved children and played with them often. This combination of factors served to give the patient the extraordinary number of 134 contacts.

A site visit to the egg plant was very helpful in formulating our approach to case-contact finding. We were originally worried that dusty, poorly venti-

lated barns might have been conducive to spreading TB, since workers might cough frequently under these conditions or have underlying occupational chronic lung disease that would predispose them to TB. To the contrary, we found that all barns were of necessity extremely well ventilated to the outside by at least a dozen large fans. Despite much dust and odor, the barns did *not* seem to create the right environment to spread TB. Moreover, there were very seldom more than two or three employees at one time in each barn containing several hundred thousand cubic feet in volume. Employees were seldom in close contact on the job; our patient's closest contacts while actually working were sporadic encounters with truck drivers, his foreman and a few other personnel.

The one high risk area on the job was a small building used by employees at break time. A room 17 feet by 11 feet by 11 feet served those who desired a rest period. Since all pay was piecemeal, employees took breaks as they chose. Therefore, not all employees rested simultaneously, and the room was used at different times by small groups. The room was entirely unventilated, except by windows and door, which were all kept closed during the cold months. It is felt that this building is where our patient's work contacts with positive skin tests were probably exposed to the greatest number of infectious droplet nuclei.

### METHODS

Skin testing was made available to all employees at the plant who desired it. Six hundred and seventy-four (97-98%) of all employees were eventually tested. The bulk of testing was done primarily for good public relations. However, because of our patient's social mobility, a certain amount of "overkill" would have been necessary in any event. Finally, the setting provided a unique opportunity to accumulate some information on the "background" number of positive skin tests in Maine and to epidemiologically link some of these positives to our patient. Tine testing was used for the majority of

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TABLE 1

DIFFERENTIAL ATTACK RATES, POSITIVE PPD		
All plant employees	33 673	4.9%
employee contacts	18 77	23.4%
employee noncontacts	15 596	2.5%
purely social contacts	5 53	9.4%
all household contacts	17 21	80.1%

skin testing, with confirmation by intermediate Mantoux PPD when positive. Greater than 5mm of induration was the criterion for a positive test, and a nurse read all tests. Very few patients remembered being previously tested, so that there were few documented converters. Of 49 patients with positive skin tests, over 30 are now on INH, with several of these hospitalized for treatment of active disease. The remainder were not treated for various reasons.

A household contact was defined as anyone who had lived in the same domicile as our patient within the last year. A social contact was seen by our patient at least twice a week, and a work contact was one that the patient saw and spoke with daily.

### RESULTS

Table 1 demonstrates that of 596 employees who were not contacts of our patient, 2.5% had a positive skin test. We would consider this a background rate and it is indeed a low one compared to some other areas of the country. This may be due to a relatively low prevalence of atypical mycobacterial infections in Maine. Employee contacts had a 23.4% positive PPD rate, nearly ten times the rate among non-contacts. Chi-square analysis in Figure 1 shows that this difference was very highly significant. When 243 teenaged part-time employees were eliminated from the analysis, because this group had a very low skin positivity (0.4%) and were all non-contacts, analysis was still highly significant. Purely social contacts of our patient had an attack rate of 9.4% and household contacts had an attack rate of 80.1%.

### DISCUSSION

Tuberculosis was a leading cause of death in the United States at the turn of the century, but it has greatly declined as a cause of morbidity and mortality since then, due to the advent of antibiotics and rigorous case-contact epidemiology by public health personnel. In Maine, only 72 new cases were diagnosed in 1976. The epidemic presented here is evidence that although TB is gradually disappearing in this country, it is still an important cause of illness in individual patients and from a public health standpoint.

Statistically, we have proven that a single patient was the source of tuberculous infection in an epidemic which involved 49 people with skin test positivity. Whereas only 2.5% of employee non-contacts were skin test positive, 23.4% of employee contacts and 80.1% of household contacts were positive. It is known that older age groups have a higher prevalence of positive PPD tests than

FIGURE 1

POSITIVE PPD VERSUS BEING AN EMPLOYEE CONTACT (PART-TIME TEENAGE EMPLOYEES INCLUDED)				
	pos PPD	neg PPD		
contact	18	59	77	
noncontact	15	581	596	$X^2 = 59.2$
	33	640	673	$p < .001$

FIGURE 2

POSITIVE PPD VERSUS BEING AN EMPLOYEE CONTACT (PART-TIME TEENAGE EMPLOYEES EXCLUDED)				
	pos PPD	neg PPD		
contact	18	59	77	
noncontact	14	339	353	$X^2 = 31.8$
	32	398	430	$p < .001$

younger age groups. However, this does not explain the differences between contacts and non-contacts in this outbreak; since our patient was young, his contacts also tended to be young. (Mean age for contacts was 27.1 years and mean age for non-contacts was 28.7 years).

We are uncertain how long our patient had primary disease before he was diagnosed, or where he contracted his infection initially. At one time he lived with an elderly couple. The husband had been diagnosed as having active TB, 10 months before our young man was discovered. Our patient went to TB clinic to have a skin test done (as a contact of the older man) but after observing the test performed on someone else, fear prevented him from being tested himself. This older gentleman could have been the source of infection for our patient. Our patient's mother gives a history of his having coughed persistently for several years, and a local drug store employee confirms this by adding that the patient kept her "out of cough drops and cough medicines" for many months before his diagnosis. At one point, we considered that a group of Vietnamese refugees who arrived at the plant in the fall of 1975 may have introduced TB into the plant area. However, the Vietnamese still present at the plant (six of an original sixteen) displayed no evidence of TB. The fact that the patient had a strain of *M. tuberculosis* sensitive to INH also provides some evidence against the theory, since many strains out of Southeast Asia are INH-resistant. Therefore, the original source of infection is undetermined.

In summary, a highly mobile 20-year-old man served as the focus for a tuberculosis epidemic, which occurred chiefly among employees at a large Maine egg farm. Vigorous epidemiology uncovered 49 PPD-positive contacts. Although tuberculosis is continually becoming rarer, it must not be forgotten when approaching a new patient. Case-contact finding on all new cases is essential and often very rewarding in preventing spread of infection.

### ACKNOWLEDGMENTS

We would like to express appreciation to Dr. Roger Condit, Farmington, Maine for referring the original patient, and to Ms. Pam Cole for clerical assistance.

# Necrologies

NORMAN E. DYHRBERG, M.D.

1919-1977

Dr. Norman E. Dyhrberg, 57, of Westbrook, Maine, one of the founders of the Westbrook Community Hospital, died in a Portland hospital on January 27 after a long illness.

Born in Falmouth, Maine on June 2, 1919, he was the son of Lauritz and Mette Dyhrberg.

He was graduated from Dana College in Blair, Nebraska and received his medical degree from the University of Nebraska College of Medicine in 1942. Dr. Dyhrberg interned at the Eastern Maine Medical Center in Bangor. He practiced in Gorham for several years, before moving to Westbrook where he practiced for 22 years, retiring in 1968 because of ill health.

He was an affiliate member of the Cumberland County Medical Society, the Maine Medical Association and the American Medi-

cal Association. Dr. Dyhrberg served for several years as the Westbrook health physician, was a Past President of the Maine Chapter, American Academy of Family Physicians, was a principal founder and former Chief of the medical staff of the Westbrook Community Hospital, and a staff member of Mercy Hospital and Maine Medical Center.

Surviving are his widow, the former Lillian Bunstock; four sons, Lauritz N. and William P. Dyhrberg, both of Westbrook, Dr. John S. Dyhrberg of Minneapolis and Thomas A. Dyhrberg of Florida; a brother, Peter N. Dyhrberg of Falmouth; two sisters, Mrs. Marie Lane and Mrs. Laura Esty, both of Falmouth; two grandchildren and several nieces and nephews.

WILLIAM V. KIRK, M.D.

1894-1977

Dr. William V. Kirk, 82, of Eagle Lake, Maine and a winter resident of Miami, Florida, died suddenly on February 21 in Miami.

He was born in Dobbin, West Virginia on November 5, 1894, the son of James N. and Calamese Kirk.

Dr. Kirk was graduated from the University of Maryland School of Medicine, Baltimore in 1917 and served an internship and residency at the St. Joseph Hospital in Baltimore. In 1920, he located in Eagle Lake where he was a Family Physician and General Surgeon for 57 years.

An honorary member of the Aroostook County Medical Society and the Maine Medical Association, he received a 50-year pin in 1967, a 55-year pin in 1972 and would have been eligible for a 60-year pin at the June 1977 annual session held in Rockport. Dr. Kirk was also a member of the American Medical Association.

Surviving are his widow, Mary Kirk; two sons, William Kirk of Rouses Point, New York and James Kirk of Miami, Florida; a daughter, Mrs. Frank Durkin of Miami, Florida; one sister, Mrs. John Dille of Roanoke, Virginia and five grandchildren.

CLYDE I. SWETT, M.D.

1902-1977

Dr. Clyde I. Swett, 75, of Island Falls, Maine, died on June 24 at a Houlton hospital following a long illness.

He was born in Bangor, Maine on June 18, 1902, the son of George I. and Lillian M. Swett.

A graduate of the University of Maine, he received his medical degree from McGill University Faculty of Medicine, Montreal in 1930, and interned at the Eastern Maine Medical Center in Bangor.

A General Surgeon, Dr. Swett had practiced in Island Falls since 1931.

He was a senior member of the Aroostook County Medical Society, the Maine Medical Association and the American Medical Association. Dr. Swett served as Councilor of the Sixth

District of the M.M.A. from 1961-1964, was a former President and Secretary-Treasurer of the Aroostook County Medical Society, a former President of the Maine Academy of Family Practice, the New England Obstetrical and Gynecological Society, and the Maine Society of Clinical Hypnosis. Dr. Swett was affiliated with the Milliken Memorial Hospital, Island Falls, the Madigan Memorial Hospital, Houlton and the Aroostook General Hospital.

Surviving are his widow, Laura Swett; one daughter, Mrs. Patricia Gideon of Bangor; one son, Anthony Swett of Caribou; ten grandchildren, three great-grandchildren and nephews and nieces.

NAPOLEON J. GINGRAS, M.D.

1911-1977

Dr. Napoleon J. Gingras, 66, of Augusta, Maine, died at his residence on July 25 after a long illness.

Born in Rochester, New Hampshire on June 27, 1911, he was the son of Fortunat and Sedulie Gingras.

Dr. Gingras was graduated from Assumption College in Worcester, Massachusetts, received his medical degree from Laval University Faculty of Medicine, Quebec in 1939, and interned in Anesthesiology at the Central Maine General Hospital in Lewiston. He had practiced in Augusta since 1940.

He served in the U.S. Army Medical Corps and later in the U.S. Air Force, and saw active duty during World War II and the Korean Conflict. Dr. Gingras was certified as a flight surgeon in 1943, and served in the National Guard between periods of active service and was war wing surgeon for the 101st Fighter Wing. He retired from the military service as a Brigadier General.

Dr. Gingras was an affiliate member of the Kennebec County Medical Association, the Maine Medical Association and the American Medical Association. He was also a member of the

American Society of Anesthesiologists, the Maine Society of Anesthesiology and the New York Academy of Sciences.

Dr. Gingras was a Past President of the medical staff at the Augusta General Hospital, Past President of the Augusta Mental Health Institute, organizer of the Anesthesia Department at the Augusta General Hospital and its President recently, and held courtesy staff membership at the Gardiner General Hospital and the Central Maine General Hospital.

Surviving are his widow, Jeanne G. Gingras of Augusta; two sons, Attorney Robert J. Gingras of Gardiner and Louis J. Gingras of Augusta; six daughters, Mrs. Lucie M. McCarthy and

Mrs. Jacqueline M. Lacasse, both of Augusta, Mrs. Jeanne Marie Audit of Montreal, Canada, Miss Pauline M. Gingras of Washington, D.C., Mrs. Helen M. Neves of Freedom and Miss Marguerite M. Gingras of Portland; a brother, Isidore Gingras of Rochester, New Hampshire; five sisters, Sister Jeannette Gingras, CSC, provincial of the Sacred Heart Province, Pittsfield, New Hampshire, Sister Marie-Ida Gingras, CSC, West Franklin, New Hampshire, Sister Anita Gingras, CSC, Rochester, New Hampshire, Sister Rose Gingras, CSC, missionary in Haiti, West Indies and Mrs. Sylvia Gareau, Rochester, New Hampshire; seven grandchildren, several nieces, nephews and cousins.

## HERMAN C. PETTERSON, M.D.

1893-1977

Dr. Herman C. Petterson, 83, of Chebeague Island, Maine, died on August 15 at his home.

He was born in Chicago, Illinois on October 12, 1893, the son of Werner and Emelie Petterson.

Dr. Petterson received his medical degree from The Hahnemann Medical College and Hospital, Chicago in 1916. He interned at the New York City Hospital and the Massachusetts Memorial Hospital, and took postgraduate courses at Harvard Medical School.

Dr. Petterson practiced in Boston from 1921 to 1953, during which time he was Chief of Pediatrics at the Massachusetts

Memorial Hospital, the St. Margaret Hospital and the Massachusetts General Hospital. In 1953, he moved to Chebeague Island and practiced there until his retirement in 1966.

An honorary member of the Cumberland County Medical Society and the Maine Medical Association, he received a 50-year pin in 1966, a 55-year pin in 1971 and a 60-year pin in 1976.

Surviving are his widow, the former Ruth Colbath; a daughter, Mrs. Robert Wieser of Newport Beach, California; a brother, Edwin of Ransom, Missouri; a sister, Mrs. Leonard Broecher of Naperville, Illinois; three grandchildren and several nieces and nephews.

## WILLIAM E. FREEMAN, M.D.

1893-1977

Dr. William E. Freeman, 84, of Yarmouth, Maine, died on September 17 at his home.

Born in West Lynn, Massachusetts on January 12, 1893, he was the son of Frederick W. and Josephine E. Freeman.

Dr. Freeman attended Bowdoin College and received his medical degree from Bowdoin Medical School in 1918. He interned and served a residency at the Lawrence General Hospital in Massachusetts, and took a postgraduate course at the New York Skin and Cancer Hospital. He practiced in Standish and Portland, located in Yarmouth in 1927, and retired in 1969 due to ill health.

An honorary member of the Cumberland County Medical Society and the Maine Medical Association, he received a 50-year

pin in 1968 and a 55-year pin in 1973. He was also a member of the American Medical Association and the American Academy of Family Practice.

Dr. Freeman served as County medical examiner and Yarmouth health officer, and was on the staffs of the State Street Hospital, the Maine Eye and Ear Infirmary and the Mercy Hospital.

Surviving are his wife, the former Geneva G. Sands of Yarmouth; a daughter, Mrs. Floyd F. Burrill of Yarmouth; a grandson, William F. Long of Yarmouth; two sisters, Mrs. Ethel Sievers of Bath and Mrs. Josephine Mathurin of Topsham; and several nieces and nephews.

# Letters to the Editor

To the Editor:

I read with interest the article entitled, "Utilization Review Chairman Speaks to the Staff" by T.F. Conneen, M.D., in the June issue of *The Journal of the Maine Medical Association*. It is indeed encouraging to see evidence for support of the PTO program for PSRO review in Maine coming from a practicing physician. The program can only be effective in its attempt to improve the quality of care when the degree of understanding and involvement by practicing physicians such as Dr. Conneen is present.

The PSRO program is far from perfect. The most effective and efficient methods of reviewing and assuring the quality of medical care are not known. However, I firmly believe that the very

deficiencies which do exist in the PSRO program lend even more strength to the arguments which support the program since physicians are in control of it. Physicians are the only ones who can put the imperfections in our methods of review and assuring quality of medical care into the total perspective of our medical care system, which is itself imperfect. We must continue to do this in the interest of the public we serve — our patients.

RICHARD T. CHAMBERLIN, M.D.  
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# County Society Notes

## Cumberland

The 413th meeting of the Cumberland County Medical Society was held at Valle's Steak House on May 19, 1977 with 101 members in attendance. It was the annual meeting, and the President, Dr. Robert E. McAfee, presided.

One application for membership received first reading — Dr. Susan A. Williams.

Second reading was given to the application of Dr. Winthrop S. MacLaughlin, and it was voted to accept Dr. MacLaughlin into membership.

The following reports were rendered during the meeting:

1. Health Career Awards — Dr. McAfee.
2. Professional Directory Committee — Dr. Goldfarb.
3. Treasurer's Report — Dr. English.
4. Medico-Legal Screening Panel Report — Dr. Drake (read by Dr. McAfee).
5. Finance Committee Report — Dr. Ray (read by Dr. McAfee).

Three resolutions were proposed:

1. . . . a resolution by Dr. William Maxwell having to do with the malpractice insurance crisis suggesting that the Maine Medical Association look into a plan for insuring the physician members of the State Association. Endorsements for the resolution were provided by the orthopedists of Cumberland County, the Maine Vascular Society, the Ear, Nose & Throat Surgeons in Cumberland County and the Maine Medical Center Radiology Associates. The resolution was carried unanimously and will be forwarded to the House of Delegates for the June meeting.

2. . . . a resolution was presented by Dr. Bruce Nelson suggesting that the administration of Medicare be kept within the confines of the State of Maine.

3. . . . a resolution presented by Dr. Sidney Branson suggesting that the proposed new headquarters of the Maine Medical

Association be located in Augusta.

The meeting was adjourned at approximately 9:35 a.m.

WESLEY J. ENGLISH, M.D., *Secretary*

## Kennebec

The Kennebec County Medical Association met at the Village Inn on May 20, 1977 having as its guests, all of the wives. Some 70 members and wives were present. A very pleasant buffet dinner was held.

Following the dinner, the members retired to the downstairs lounge where music and dancing was enjoyed by those who wished.

A brief business meeting was held resulting in the election of the following officers: Drs. Richard E. Barron, President and Valentine J. Moore, Vice President. The new Councilor is Dr. Robert A. Stram.

Further actions of note which should be recorded in the minutes include the transfer of Dr. George Davis and Dr. William Bristol from the respective counties of Androscoggin in Maine and Kalamazoo in Michigan.

The Kennebec County Medical Association met at the John Martin Manor Restaurant in Waterville on September 13, 1977. There were forty-six members and guests in attendance. Following a pleasant cocktail hour and a very nice meal, the minutes of the preceding meeting were dispensed with.

Correspondence from the Maine Medical Association regarding the JUA and the hearing on National Health Insurance were read. Applications from Dr. Herman and Dr. Becker were read. There being no further business, Dr. Barron introduced the speaker, Dr. Richard Spark of the Beth Israel Hospital, who

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presented a most provocative discussion of the benefits and drawbacks of annual examinations and multiphasic types of examinations.

The meeting was adjourned at 10:00 p.m.

O. THOMAS FEAGIN, M.D., *Secretary*

### Hancock

The Hancock County Medical Society met at the Hilltop House in Ellsworth, Maine on Wednesday, June 1, 1977.

The meeting was called to order after dinner by the President, Dr. John D. McIntyre. He introduced the speaker of the evening, Dr. John S. Kaiser of Bangor, who spoke on melanomata, their recognition, management, and treatment. This was a very stimulating and practical presentation.

Following his address, a business meeting was held with the minutes of the previous meeting read and approved. Dr. Richard C. Leck, President of the Maine Medical Association, was then introduced and gave a complete discussion of "Certificate of Need Legislation" presently before the Legislature of the State of Maine. A spirited discussion then ensued regarding aspects of the presently proposed bills. As non-members were present during the meeting, Dr. John R. Tyler motioned that these individuals be invited to speak and participate in the discussion. The motion was seconded by Dr. Morris A. Lambdin, and with a tie vote resulting, the motion failed for lack of majority vote. Subsequently, a motion was made by Dr. Sucsy and seconded by Dr. Tyler that the Hancock County Medical Society oppose any extension of "Certificate of Need Legislation" into the physician's offices. Again, after discussion, this motion was voted with 11 favoring and one against.

Turning to other matters, Dr. Randall H. Silver made the announcement that for those who are dealing with the Maternal and Child Health Program that there is now a new fee schedule and forms to be used in submitting bills to the program.

Under other old business, Dr. Tyler sought some discussion of the present malpractice problems in the State. Dr. Leck outlined the present status of joint underwriting and malpractice laws in the State. Dr. Leck agreed to discuss with Mr. Charles Cragin of the Maine Medical Association the possibility of steps that the local or State Association could take in regard to the cancellation of a member's insurance without due cause or other suitable alternatives for insurance coverage.

A motion was made by Dr. Lambdin and seconded by Dr. Quinby D. Gurnee that physicians who presently sponsor a Physician's Assistant be allowed to invite these individuals to the next meeting of this Society. After discussion, the motion failed by a vote of 5 in favor and 6 against.

The meeting was then adjourned with the agreement that the next meeting date be established and called by the Executive Committee.

The following are the minutes of the meeting of the Hancock County Medical Society held at the Golden Anchor Inn in Bar Harbor on September 7, 1977.

There were 10 members, 4 non-members and 5 guests present.

The meeting was called to order by the President, Dr. John D. McIntyre, and the following matters were brought up for discussion.

1. Medical examiner laws. The responsibilities and functions of all physicians in the county were discussed in this regard.

2. Membership problems of the county and state society. Dr. McIntyre discussed the value of association of both the county and state societies and membership was solicited.

There being no further old business, the speaker of the evening was introduced, Mr. William Brines, who spoke of regionalization of medical care, particularly as applied to medical practice in Hancock County. This was an enlightening message with much discussion following concerning concepts of the centralization and regionalization of health care delivery on the local level and the influence of Federal and State planners in this regard.

The meeting was adjourned with plans for the next meeting to be determined by the Executive Committee.

WILLIAM C. BROMLEY, M.D., *Secretary*

### Washington

A clinical meeting of the Washington County Medical Society was held on June 15, 1977 at the Lincoln House Inn, Dennysville, Maine, with ten members and four guests present.

Following an excellent meal, Dr. Jean J. Labelle, Plastic Surgeon of Portland, Maine spoke on "Reconstructive Surgery for Rheumatoid Arthritis," particularly that involving the hand. Dr. Labelle showed slides, illustrating the corrective surgery that could be done. He also brought samples of a plastic prosthesis used in this corrective surgery. He stated that this corrective work could be done at any age and would benefit the patient both physically and mentally. He found that it was best to treat these patients by a "team effort," including Rheumatologist, Plastic surgeon, Physiatrics and Ancillary personnel. He stated, that, as yet, this type of approach had not been widely used, but as it became better known it would probably find much greater use. Patients generally had been greatly benefited by this type of treatment. He stated that they did very little surgery on synovial membranes, since this seemed to be better treated by use of corticosteroids.

KARL V. LARSON, M.D., *Secretary*

### DRUG THERAPY REVIEWS — Intravenous Fluid Therapy

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# The Journal of the Maine Medical Association

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## Electrocardiographic Monitoring of Cardiac Arrhythmias in Ambulatory Patients

JOE R. WISE, M.D., KATHLEEN TAMM, R.N. and WILLIAM S. WILSON, M.D.\*

Cardiac arrhythmias are often difficult to document. Frequently these rhythm disturbances, though symptomatic, are transient, have subsided by the time an electrocardiogram can be performed and do not recur during the usual 45 to 60 second recording period. The experience provided by intensive care units has established the value of continuous electrocardiographic monitoring in the detection of arrhythmias. During the past several years, techniques have been developed which permit the continuous recording and analysis of arrhythmias occurring in ambulatory patients. The initial efforts at monitoring the electrocardiogram continuously by radiotelemetry have been replaced by specially designed systems using magnetic tape recorders.<sup>1,2</sup>

The Holter system uses a small (four pounds) battery operated tape recorder connected by electrodes to the patient's chest and contained in a case worn over the shoulder (Fig. 1). During the recording period, usually twelve to twenty-four hours, the patient is encouraged to go about his usual routine and maintain a diary of his activities. The completed tapes are scanned on a high-speed play-back unit which permits review of the twenty-four hour tape in twenty-four minutes (Fig. 2). Changes in the electrocardiogram displayed on the scanner are detected visually and standard rhythm strips are recorded for review and analysis. The electrocardiographic changes are correlated with the patient's activity and symptoms as noted in the diary.

Ambulatory monitoring may be indicated when detection and identification of cardiac arrhythmias are considered important in the patient's management. Extensive experience with the Holter



Fig. 1. Portable electrocardiogram recorder connected to chest electrodes and worn over the shoulder during the recording period.

monitoring system in a wide variety of circumstances has been reported.<sup>3-12</sup> For the past 2 years at Eastern Maine Medical Center, we have been using the Holter system in the evaluation of patients who have, or are suspected of having, cardiac ar-

\*From the Cardiology Section, Medical Service, Eastern Maine Medical Center, Bangor, Maine 04401.

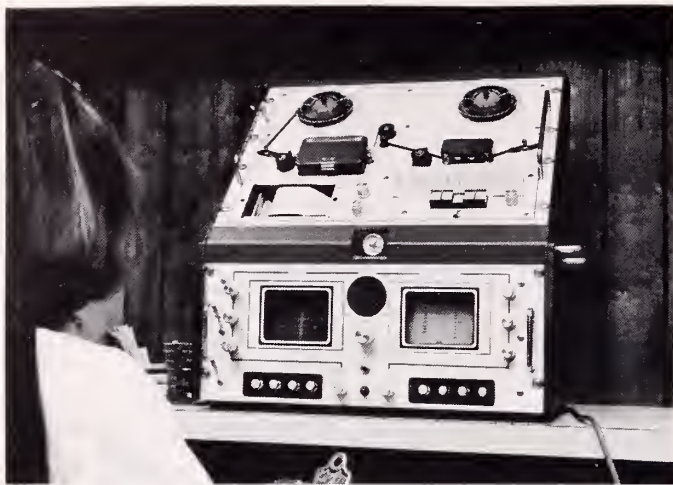


Fig. 2. High-Speed playback scanner permits rapid review of the taped recordings. Pertinent sections of the record are printed on standard EKG paper and mounted for review.

rhythmias. The following section deals with some of the clinical situations in which we have found this technique helpful during that time.

### CARDIAC ARRHYTHMIAS

#### *Supraventricular Tachycardia*

The standard electrocardiogram provides a 45 to 65 second sample recording and is often inadequate for the identification of intermittent or transient arrhythmias.<sup>6</sup> The Holter recording system allows analysis of over 1000 times as many EKG complexes during an observation period long enough to include not only sleep, but also potentially provocative activities. Episodes of supraventricular tachycardia including atrial tachycardia, atrial fibrillation and atrial flutter, are often paroxysmal and the symptomatic disability of patients with these rhythm disturbances may vary widely from worrisome palpitations to prostration. Documentation and specific identification of these rhythm disturbances is important, not only to help in the selection of the proper treatment, if any, but also to exclude more serious arrhythmias.

#### CASE 1

R. S., a 59-year-old teacher, was admitted to the hospital for an evaluation and treatment of increasing angina. No evidence of infarction occurred. Exercise tolerance by treadmill exercise test was fairly good and he was discharged taking Inderal® and Isordil®. During his follow up, he complained of frequent episodes of "fluttering" in his chest associated with some lightheadedness. Resting electrocardiogram showed only sinus rhythm with no evidence of arrhythmia or ectopic beats. A Holter monitor recording showed several runs of intermittent atrial fibrillation (Fig. 3). Lanoxin® was added to his treatment and no further palpitations have occurred.

#### *Ventricular Arrhythmias*

Recent studies have suggested that ventricular ectopic beats are a potential risk factor for sudden death in patients with coronary artery disease.<sup>12,17</sup> Because of the long sampling period of ambulatory

activity, the Holter monitor system has been used extensively in studying these patients.

The demonstration of ventricular ectopic beats during the late hospital phase of acute myocardial infarction appears to identify a group of patients at a higher risk of sudden death after discharge. In one study, all patients died suddenly who had ventricular ectopy during their hospitalization, whereas, those without ventricular arrhythmias all survived the two-year follow up period.<sup>12</sup> The absence of ventricular arrhythmias during the stay in the coronary care unit did not exclude their occurrence in the late hospital phase. The occurrence of late arrhythmias did correlate with evidence of left ventricular dysfunction. Standard electrocardiograms were relatively insensitive in detecting these rhythm disturbances compared with the Holter system. Patients free of ventricular ectopy by serial standard electrocardiograms had a 62% incidence of serious forms of ventricular arrhythmia and a 6% incidence of ventricular tachycardia during continuous ambulatory monitoring prior to discharge.<sup>12</sup> Since these late, potentially lethal rhythm disturbances cannot be accurately predicted by monitoring in the coronary care unit, their detection will depend on more vigorous use of ambulatory monitoring in the hospital prior to discharge.

On rare occasions, sustained ventricular tachyarrhythmias can be intermittent and self-terminating. Usually these rhythm disturbances are associated with a fall in blood pressure and cerebral symptoms such as faintness, syncope or seizures. Many types of cardiac arrhythmias can be associated with cerebral dysfunction and, since treatment may vary widely, specific identification of the rhythm disturbance is necessary.

#### CASE 2

A. B., a 70-year-old man, was admitted to the hospital on several occasions for the evaluation of recurrent syncope. No rhythm disturbance had been documented and neurological evaluation was normal. The resting EKG showed only occasional premature ventricular contractions and signs of an old anterior infarction. Intermittent complete heart block was suspected and a permanent pacemaker was being considered. A Holter monitor recording showed recurrent episodes of ventricular tachycardia. Pronestyl® was begun and no further syncope occurred.

#### *Sinus Node Dysfunction - (Sick Sinus Syndrome, Bradycardia-Tachycardia Syndrome)*

Some patients with recurrent episodes of supraventricular tachycardia have associated periods of sinus bradycardia and/or sinus arrest as well. This troublesome combination of rhythm disturbances is being seen with increasing frequency, especially, in older patients, and has been referred to by a variety of names including sick sinus syndrome, bradycardia-tachycardia syndrome and sinus node dysfunction.<sup>13,14</sup> Symptoms vary and may be produced by the tachycardia (palpitation, breathlessness, weakness) or the intermittent and often marked bradycardia (dizziness, syncope). Patients

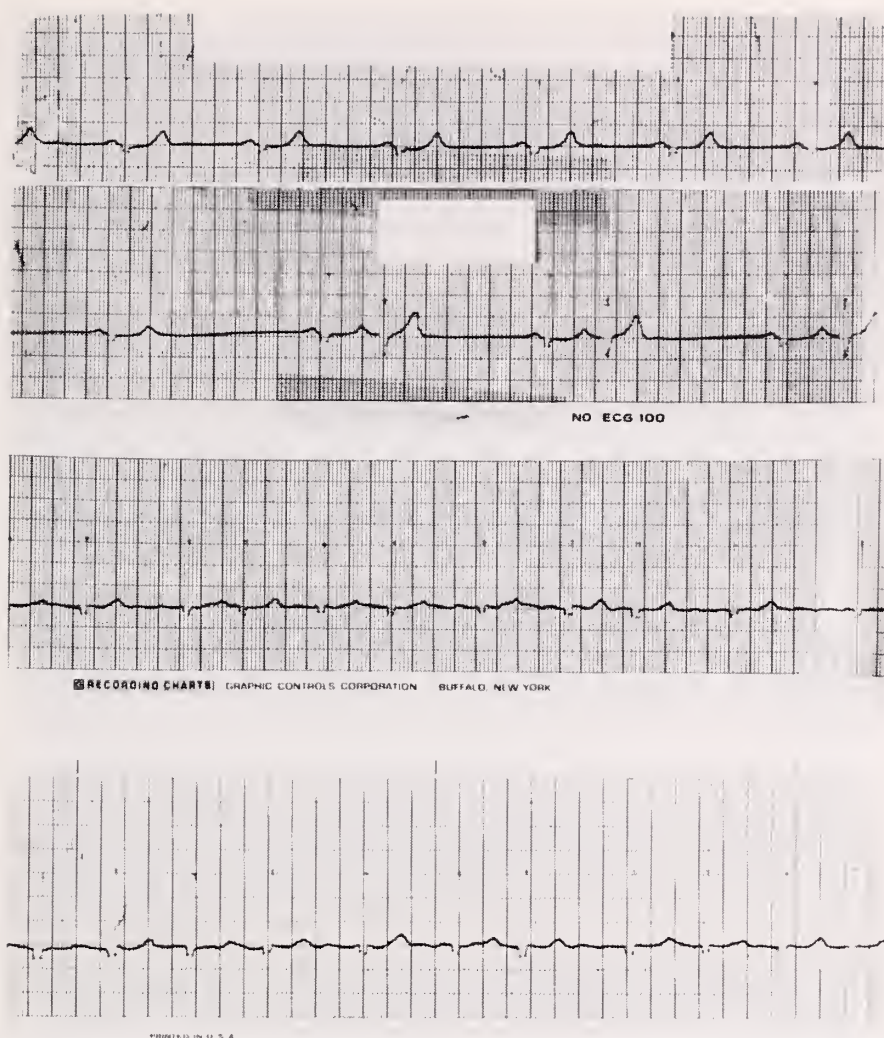


Fig. 3. Case 1, Top Strip: Control recording showing sinus rhythm. During recording period supraventricular ectopic beats (second strip) and runs of atrial fibrillation (third strip) were noted.

with the bradycardia-tachycardia syndrome are often older and differentiation from cerebrovascular disease may be difficult. In many of these patients, the electrocardiogram between attacks is frequently normal and prolonged monitoring may be required to document the arrhythmia. Drug therapy alone often does not provide adequate control of these rhythm disturbances and permanent cardiac pacing is frequently required.<sup>15,16</sup>

#### CASE 3

L. P., a 60-year-old man, had an acute anterior myocardial infarction in February of 1973. In May of 1977, he was hospitalized for evaluation of unsteadiness and dizziness and at least on episode of syncope in which he sustained multiple rib fractures. Extensive neurological evaluation was negative. Numerous resting electrocardiograms showed signs of old anterior infarction with sinus rhythm and no evidence of arrhythmia. Holter monitor recording showed apparent sinus node dysfunction with episodes of supraventricular tachycardia and bradycardia, sometimes in response to tachycardia and sometimes appearing spontaneously with rates as slow as 40 per minute (Fig. 4). A permanent transvenous pacemaker was implanted and no further episodes of dizziness or syncope have occurred.

#### CASE 4

C. S., a 76-year-old man, was admitted for evaluation of dizziness and transient syncope. Associated problems included angina pectoris and one previous episode of complete AV dissociation with narrow QRS. The episodes of dizziness and faintness had been lasting for several minutes during which time he had to put his head down on his desk waiting for the episode to pass. He was not aware of his heart rate during these episodes. His cardiac examination was within normal limits except for fourth heart sound. His chest x-ray showed moderate left ventricular enlargement. A resting electrocardiogram showed signs of old inferior infarction with prolonged PR interval of 0.28. Neurologic evaluation and monitoring in the intensive care unit did not reveal the cause for his dizziness. Holter monitor recording showed episodes of sinus arrest up to 3.5 seconds (Fig. 6). A permanent transvenous pacemaker was subsequently implanted.

#### EVALUATION OF SYNCOPY AND CEREBRAL SYMPTOMS

Continuous electrocardiographic monitoring can be very helpful in the evaluation of patients with cerebral symptoms such as lightheadedness, dizziness, or syncope.<sup>7</sup> Sometimes these symptoms are related, not to primary central nervous system dis-



Fig. 4. Case 2, Top Strip: Control recording shows sinus rhythm. Intermittent supraventricular tachycardia (second & fourth strips) and marked sinus bradycardia recurred during the recording period.

ease, but to the reduction in cerebral blood flow that occurs with some cardiac arrhythmias.<sup>19</sup>

In one recent study, 358 patients with intermittent dizziness or syncope were evaluated with the Holter monitor. None had evidence of "pertinent" arrhythmia on the resting electrocardiogram. Thirty-two percent of those monitored demonstrated during the recording period an arrhythmia known to be associated with dizziness or syncope. An additional 40 patients (11%) had short duration arrhythmias that were not associated at that time with symptoms, but were capable of producing symptoms if sustained (ie. supraventricular or ventricular tachycardia of less than six seconds duration, asystole less than 2 to 4 seconds in duration.) Prolonging the monitoring period from twelve to twenty-four hours increased the detection of "pertinent" arrhythmias from 13 to 23%.

In a similar study of 39 patients with symptoms of cerebral ischemia, Walter found 10 patients (25%) with cardiac arrhythmias that could have accounted for these symptoms.<sup>20</sup>

Rapid arrhythmias such as supraventricular and ventricular tachycardia can cause cerebral symptoms due to transient drops in cerebral blood flow. Often, however, the rhythm disturbance is a bradycardia, either related to sinus node disease or complete heart block. It is important to appreciate that symptomatic heart block is not always permanent, but that it may be intermittent or transient. Patients may develop transient complete heart block or have an Adams-Stokes attack and recover so that the

heart rate is normal at the time of a subsequent examination. For many of these patients, a permanent pacemaker is indicated.<sup>7,22</sup>

#### CASE 5

G. P., a 70-year-old woman, was evaluated for recurring episodes of faintness of several months duration with one episode of syncope. She had been previously, and was otherwise, asymptomatic. The electrocardiogram at rest revealed only slightly prolonged PR interval of 0.24 seconds. Neurologic evaluation was normal. Holter monitor recording revealed episodes of transient complete heart block (Fig. 7). A permanent transvenous pacemaker was implanted and no further episodes of faintness or syncope have occurred.

#### CHEST PAIN SYNDROMES

In addition to evaluating rhythm disturbances, ambulatory electrocardiographic recordings have been used in the detection of ischemic ST and T-wave changes in patients with coronary artery disease. Stern and Tzivioni, using a continuous recording system, showed that dynamic changes do occur in the electrocardiogram with emotional and physical stress in patients who have normal resting electrocardiograms and negative Master's tests. In 37 of the patients who showed ST-T wave changes during the 24-hour monitoring period, one developed an acute myocardial infarction, 16 reported worsening of chest pain and 7 developed abnormal changes on the resting electrocardiogram in the 6 to 12 month follow up period.<sup>10</sup> None of those events occurred during the same time in 43 patients with no ST-T wave changes during the Holter monitoring.

Caution must be used in the evaluation of ST-T

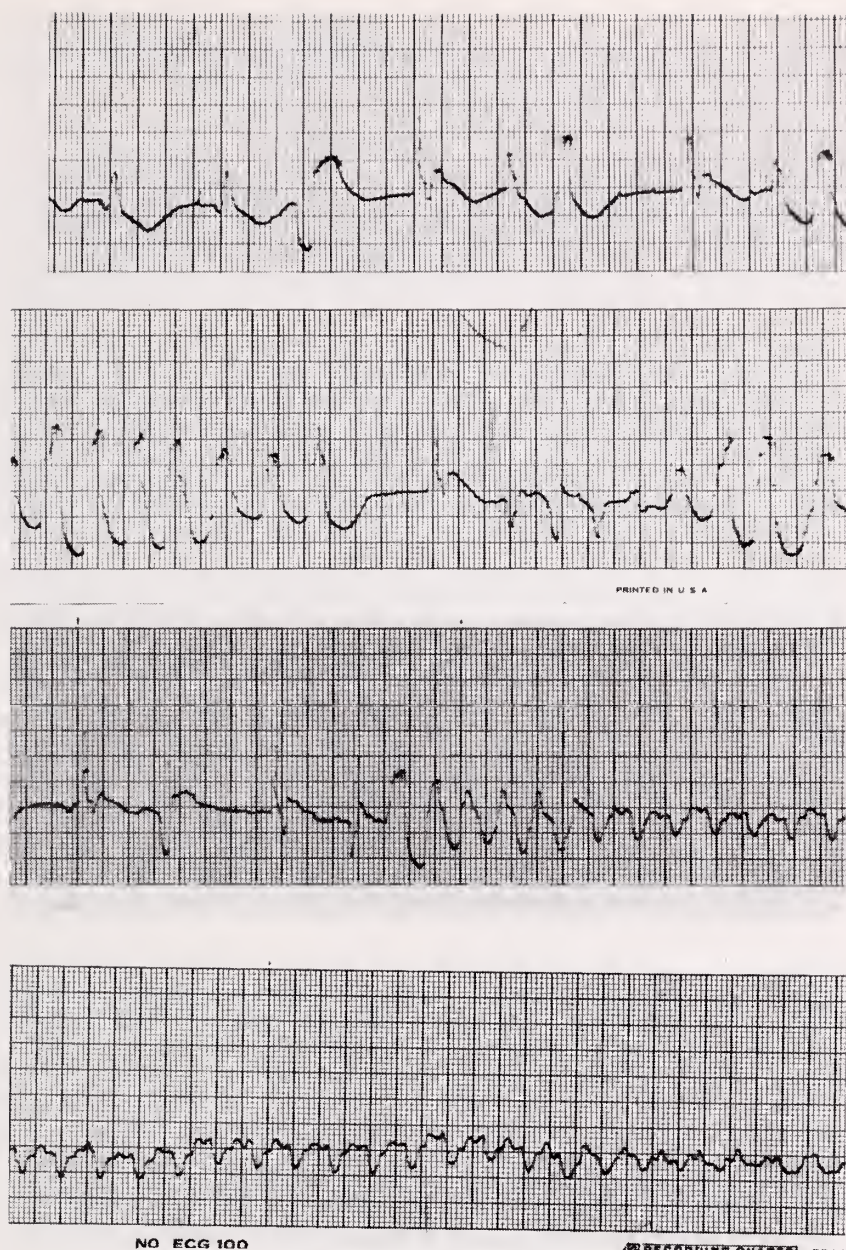


Fig. 5. Continuous recording. Fatal ventricular tachycardia — fibrillation.

wave changes under these circumstances, however, since similar changes can occur with changes in body position.<sup>23</sup> In addition, ischemic chest pain may occur without ST-T wave changes on the ambulatory electrocardiogram since the limited lead system used may not be extensive enough to record such changes. The continuous monitoring system may be helpful if the chest pain and electrocardiographic changes occur simultaneously and it may be of some assistance in the evaluation of chest pain occurring with emotional distress or during sleep (Fig. 8).

#### OTHER USES

Ambulatory electrographic monitoring can be

used to evaluate the effectiveness of antiarrhythmic drug therapy. Proof of effectiveness is particularly important when rhythm disturbances are life-threatening ones or the drugs being used are costly and/or potentially toxic.

Monitoring during special activities such as driving, work, sports and sexual intercourse can provide evidence on which to base better advice to patients with cardiac disease with regard to activity restrictions.

Patients with suspected pacemaker malfunction require close and often prolonged monitoring of the electrocardiogram. Previously, if the ordinary electrocardiogram was not diagnostic, these patients had to be admitted to the hospital for observation,

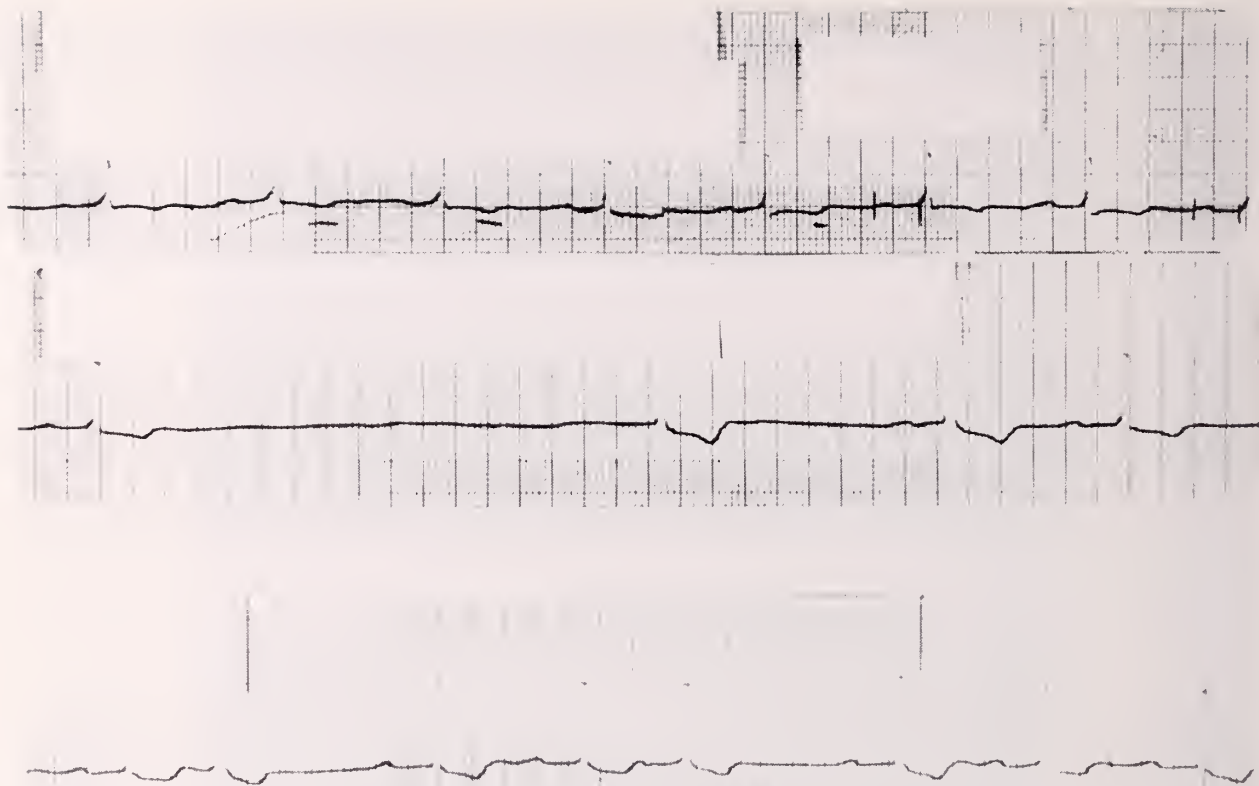


Fig. 6. Case 4: Control recording (top strip) shows sinus rhythm. Sinus arrest with pauses of 3-3.5 seconds (second strip) recurred during the recording period.

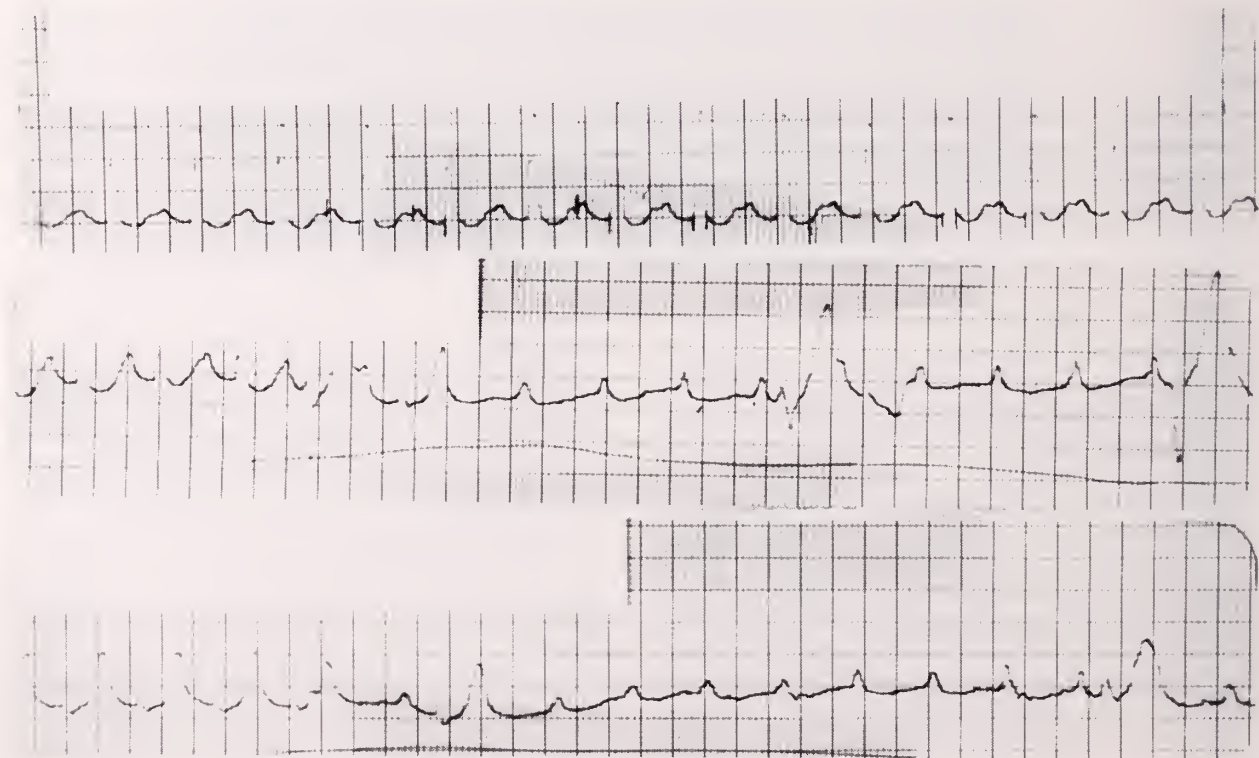


Fig. 7. Case 5: Control recording shows sinus rhythm (top strip). Later in the tracing (second and third strips) there were several periods of intermittent complete heart block.

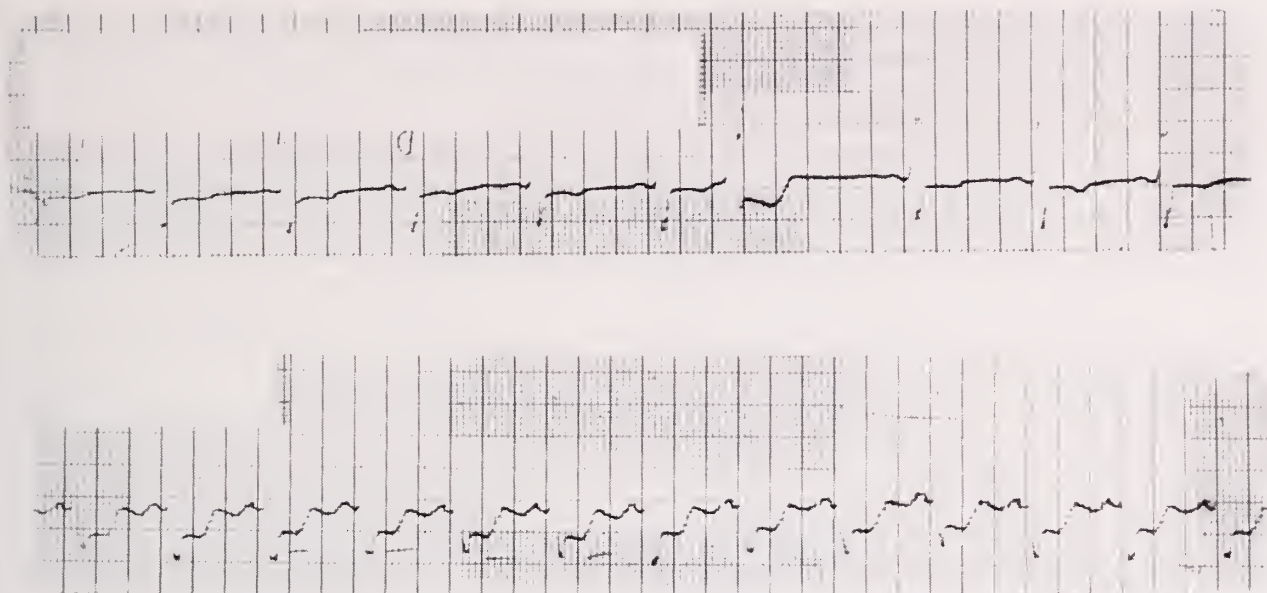


Fig. 8. Compared to the control tracing (top strip), marked ST segment depression occurred intermittently during the recording period, (second strip).

often in the coronary care unit with its attendant expense and activity restriction. The ambulatory monitoring system with its long recording period is very helpful in this situation and permits usual activities.

### CONCLUSION

The Holter recording system is a valuable extension of the electrocardiogram. It is very sensitive and has been particularly helpful in the evaluation of arrhythmias and other electrocardiographic abnormalities which may be transient or intermittent. In addition, it has made possible the objective evaluation of treatment and management of patients with cardiac arrhythmias. Since it can be worn about, the monitoring period can include usual and provocative activities and the patients need not be confined in a coronary care unit.

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**Warnings:** Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

**Use in Pregnancy:** Thiazides cross placental barrier and appear in cord blood; in pregnancy, weigh anticipated benefit against possible hazards to fetus, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

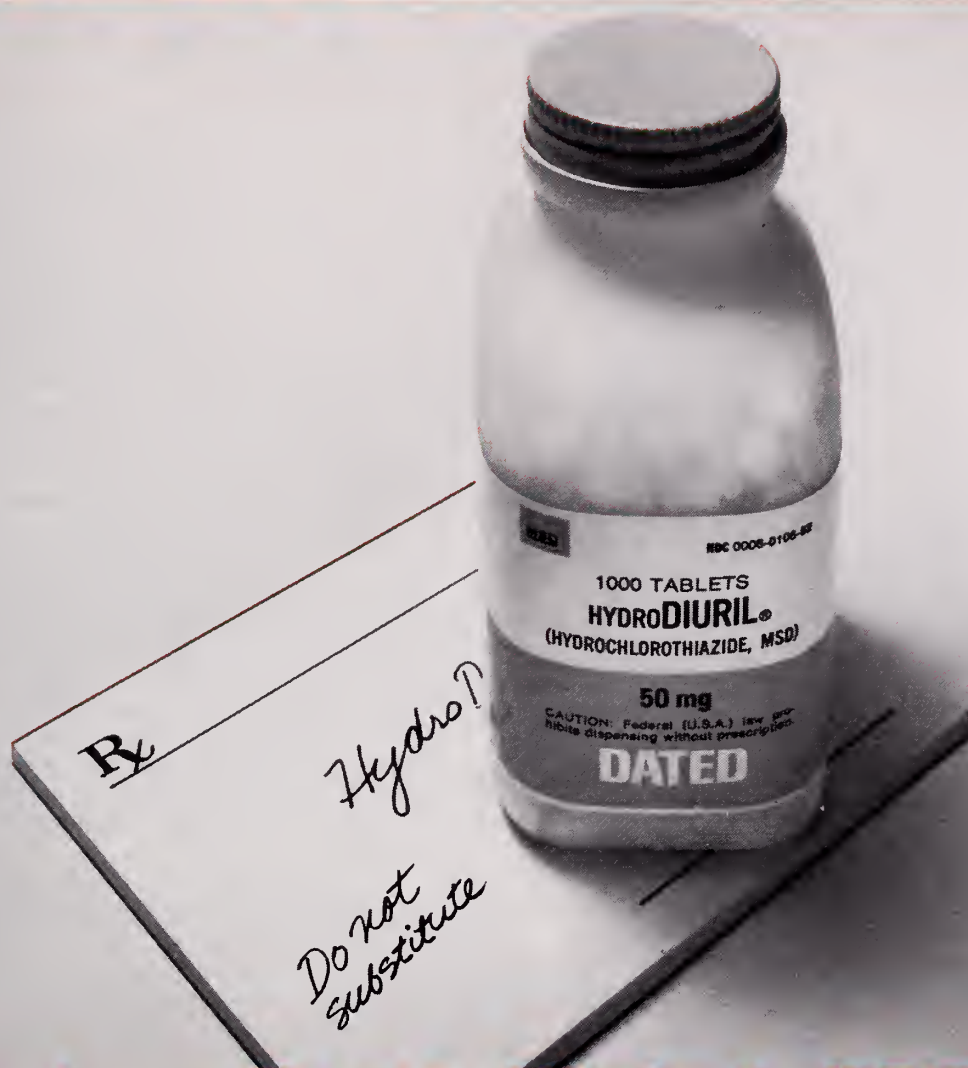
**Nursing Mothers:** Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

**Precautions:** Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting ex-

cessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in post-sympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal im-

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pairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

**Adverse Reactions:** *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis. *Central Nervous System*—Dizziness; vertigo; paresthesias; headache; xanthopsia.

*Hematologic*—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

*Cardiovascular*—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

*Hypersensitivity*—Purpura; photosensitivity; rash; urticaria; necrotizing angitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.

*Other*—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

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# Too Many Ruptured Aneurysms

DAVID M. SENSENIG, M.D.\*

A ruptured abdominal aortic aneurysm poses a sudden emergency situation requiring the fastest mobilization of surgeons, assistants, anesthesiologists and operating room personnel possible, plus large amounts of blood. When the patient reaches the hospital alive, he usually has no better than a fifty percent chance of survival. Obviously, elective resections are preferable, but the diagnosis is not always apparent. The following report is a case in point.

## CASE REPORT

A man, age 62, had a chronic problem with ulceration of the left leg due to a continuation of post phlebitic syndrome and peripheral vascular insufficiency. He was quite obese with a large abdomen. He had been treated for a while with ointments and supportive dressings without improvement, so he was referred for any additional help possible. The use of Coumadin® with moderate prolongation of prothrombin time to 1½ to 2x control values was instituted as an additional therapy. This proved to be beneficial so that the ulceration healed. The patient was maintained on Coumadin and was seen from time to time to check on his status. Prothrombin checks were performed every two weeks. At one point, a KUB film was done. It was normal except for some aortic calcification. Aneurysm was not suggested by the radiologist. Months after being first seen by the author the patient developed extremely severe left lower quadrant pain and fainted. He was rushed to the hospital where a diagnosis of a ruptured abdominal aortic aneurysm was made. Blood was cross-matched and emergency surgery was undertaken. At operation, a resection of a ruptured abdominal aneurysm was carried out with replacement with a bifurcated Dacron graft. Fortunately, the patients' renal function was satisfactory. He was left on the respirator for a few days but was able to be weaned from it. Recovery was progressive so that the patient could be discharged on the fifteenth postoperative day. He was subsequently checked in the private surgical office and has continued to do well.

## DISCUSSION

The operation of resection of an abdominal aneurysm can be done electively with a low post-operative mortality, probably in the range of 5%. There is time to assess pulmonary function and partially correct chronic bronchitis by preoperative use of intermittent positive pressure breathing, bronchodilators and pulmonary physiotherapy. Cardiac reserve can be evaluated, digitalis administered if indicated and diuretics used if need be. Kidney function can be studied and dehydration corrected. The patient can be sent to the operating room in the best possible fluid and electrolyte balance. An intravenous infusion can be given after midnight so that the patient is not dehydrated when he reaches the operating room the next morning at 8:00 A.M. Prophylactic antibiotics can be administered prior to surgery. The operating team is well organized for

a planned operation in the morning when the personnel are alert and rested.

Contrast this with the patient with a ruptured abdominal aortic aneurysm. He may be in shock with pronounced vasoconstriction due to circulating catecholamines, an anemia of unknown severity, a certain degree of renal tubular insult, and perhaps an ischemic myocardium as a result of the superimposition of a lowered aortic diastolic pressure upon his atherosclerotic coronary arteries. The true cardiac status prior to rupture may be unknown as a result of the unavailability of records from the referring physician at some wee hour of the morning. The patient probably had back pain and took a lot of aspirin containing analgesics which effectively knocked out platelet function for the next seven to ten days so that much more blood is required intraoperatively. Moreover, the patient may have a rare blood type which is difficult to get on short notice at 2:00 A.M. Large amounts of non-colloidal solutions are given during resuscitation aggravating adult respiratory distress syndrome. It is an entirely different ball game with the Grim Reaper having quite a few runs before the surgeon even comes to bat. The cost of treating a ruptured aneurysm is much more than an elective one, considering the stay in intensive care, multiple blood transfusions, respiratory care, and so forth.

Where do we stand in Eastern Maine with this problem? A review of abdominal aneurysms treated at Eastern Maine Medical Center over the past three years showed that twenty-one of fifty-seven resected aneurysms were ruptured. Hopefully, nine out of ten should not be ruptured. It this seems too much to hope for, four non-ruptured out of five should be an attainable goal. How can we physicians help to achieve this goal? The family physician is perhaps the one most able to help in this regard. He should realize that elective resection carries low mortality and that the presence of a non-resected aneurysm is as dangerous as a non-treated malignancy. Statistics vary but it is probably fair to state that one-half of the aneurysms over 5 cm. in diameter will rupture within two years with at best a fifty percent survival in those who reach the hospital alive, and many do not. This means that attention must be paid to palpitation of the abdominal aorta when doing an annual physical examination especially in those over age fifty. A good way is to approach the aorta from the right with the fingers of the left hand and from the left with the fingers of the right hand until pulsation is felt. Then the space between the fingers can be measured. If it is over 3

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*Continued on Page 458*

# Gastroduodenal Varices Secondary to Splenic Vein Thrombosis

CHARLES T. LYNCH, Jr., M.D.\* AND DON L. MAUNZ, M.D.\*\*

Gastroduodenal varices, when associated with esophageal varices and portal hypertension are a commonly encountered cause of gastrointestinal blood loss, and lend themselves readily to diagnosis. Less well known, however, is the situation where gastroduodenal varices may result from occlusion of the splenic vein, therefore existing in the absence of portal vein hypertension. Such varices may also be a source of chronic or acute gastrointestinal blood loss. Not only is this situation much less common, but it is also much more difficult to diagnose, because of the usual absence of the more easily recognized esophageal varices, and because of the lack of the many clinical stigmata which usually accompany portal hypertension.

Furthermore, failure to establish this diagnosis means missing a curable form of gastrointestinal blood loss, or may result in subjecting a patient to very hazardous surgery, because of the unrecognized venous engorgement which the surgeon will encounter during an exploratory operation.

The following case report of a patient recently seen at Eastern Maine Medical Center will serve to illustrate many of these points.

## CASE REPORT

L. C. is a 68-year-old white male, first admitted to the hospital on March 17, 1977, with a three-year history of anemia, non specific abdominal pain and occasional tarry stools. There was a history of alcohol abuse. He had been evaluated previously for this problem, with reportedly normal barium studies. On the day of admission, he had passed a tarry stool and felt lightheaded. Physical exam was unremarkable. Stool guaiac exam was positive for blood. The hematocrit, which was 40% on admission, soon fell to 29%. Upper GI series revealed some prominent mucosal folds in the duodenum (Fig. 1), but was otherwise unremarkable. The patient was transfused and placed on a peptic ulcer regimen, becoming asymptomatic with a hematocrit of 33%.

The patient was discharged, but returned on April 4, after again developing tarry stools and lightheadedness. The hematocrit at this time was 22%. He was again transfused, with improvement in the hematocrit. Endoscopy revealed a normal stomach and duodenum. An upper GI series again revealed only prominent mucosal folds in the duodenum. An abdominal angiogram, including a selective celiac axis injection, failed to reveal any bleeding site, but did show a large spleen, occlusion of the splenic vein, varices in the gastric fundus, and a patent portal vein (Fig. 2). A venous catheterization was performed, demonstrating a normal hepatic venous wedge pressure of 20 cms. H<sub>2</sub>O (reflecting a normotensive portal vein).

In the absence of hematemesis or gastric aspirate containing blood, the gastric varices were not immediately accepted as the



Fig. 1. Spot film of the barium filled duodenum showing thickened mucosal folds in the immediate post-bulbar area.

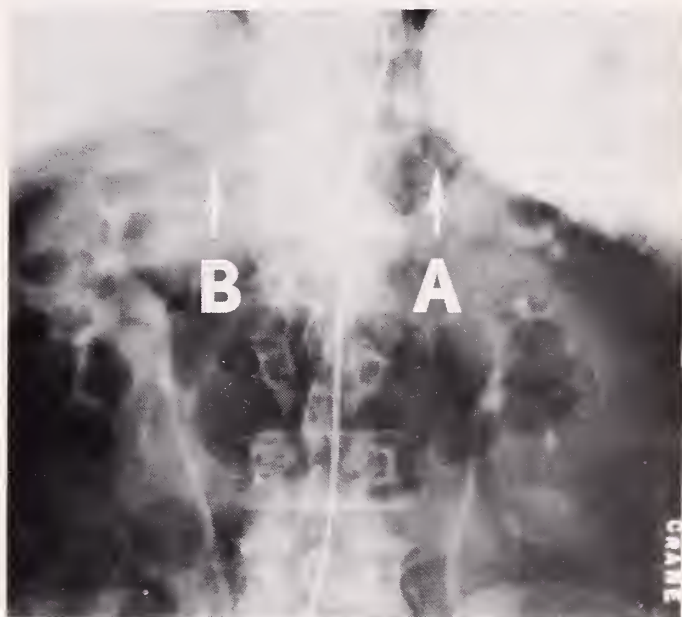


Fig. 2. Late venous phase film from injection of the celiac axis, showing varices in the region of the gastric fundus (A) and a patent portal vein (B).

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cause of the occult bleeding, though it was suspected that the prominent duodenal mucosal folds might represent varices, and that these could be the source of blood loss. Because of the uncertainty and the failure to clearly visualize any duodenal

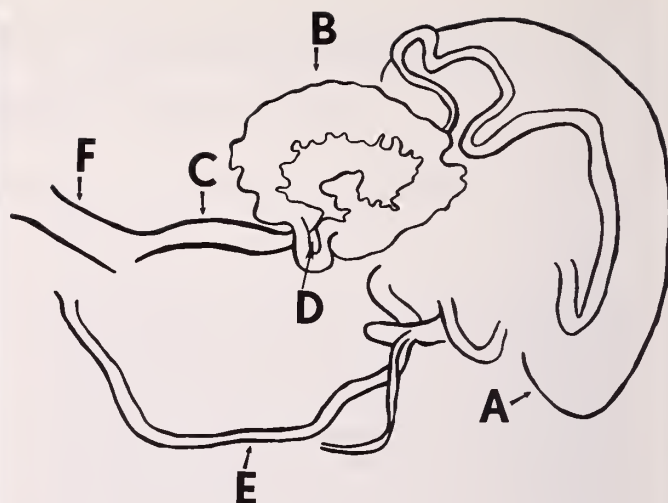


Fig. 3. Splenoportogram film on left is explained by diagram on right. (A) Spleen. (B and D) Varices in gastric fundus. (C) Coronary vein draining varices. (E) Right gastroepiploic vein. (F) Portal vein.

varices at angiography, it was decided to discharge the patient, with the intent of performing splenoportography, should he continue to bleed.

The patient became symptomatically anemic again on May 16, and was readmitted at this time. The hematocrit was 23%. Endoscopy of the stomach and duodenum was again negative. Splenoportography confirmed the previous impression of an occluded splenic vein, a widely patent portal vein, and clearly demonstrated the varices in the stomach as well as the duodenum. (Figs. 3 and 4) Splenic pulp pressure was 30.5 cms. H<sub>2</sub>O.

At laparotomy, the liver appeared normal, while the spleen was enlarged. Collateral venous channels were noted in the peritoneal ligaments of the spleen. The left gastroepiploic vein was unusually large. The pancreas was encased in dense fibrous tissue. Catheters were simultaneously placed in the portal vein and in the left gastroepiploic vein near the splenic hilum, revealing a splenic venous pressure 8 cms. H<sub>2</sub>O higher than portal pressure. Splenectomy was performed and biopsies of the liver and pancreas obtained. These revealed a normal liver and chronic pancreatitis. The spleen weighed 400 grams and showed sinusoidal congestion.

Following surgery, the patient has maintained a stable hematocrit and has remained asymptomatic.

### DISCUSSION

The consequences of splenic vein occlusion were first described many years ago, but several recent reports emphasize the continuing difficulty in recognizing the disease complex.<sup>2,8,10,11</sup> Normally, blood from the spleen drains into the splenic vein and thence directly into the portal vein. Emptying into the splenic vein are the short gastric veins which drain the gastric fundus. Some of the venous drainage from the gastric fundus also empties into the coronary vein, which in turn empties into the portal vein or the splenic vein near its confluence with the portal vein. The splenic vein is in contact with the pancreas for much of its course. Should anything obstruct the course of the splenic vein, splenic blood will drain through the short gastric veins to the gastric fundus, from there to the coro-



Fig. 4. Splenoportogram film two seconds after Fig. 3 reveals duodenal varices. (arrows).

nary vein, and thence to the portal vein. This large volume of blood imposed upon the veins of the gastric fundus will cause engorgement of the veins, resulting in varices of the gastric fundus. Varices may also form in the body of the stomach, or even in the duodenum. These varices may also prove to be a source of blood loss.<sup>1</sup>

Since the portal vein is still patent and normotensive, esophageal varices are rarely formed, as the veins of the lower esophagus are usually free to drain into the patent coronary and portal veins. There have been, however, reports of isolated splenic vein occlusion with gastroduodenal varices which have also had associated esophageal varices, even in the face of a normotensive portal vein.<sup>10,11</sup> It is assumed in these cases that the hypertensive

splenic vein, in accomplishing its decompression, has availed itself of additional collateral pathways through the submucosal veins of the lower esophagus. These reports are at variance with those of other authors<sup>1,8</sup> who feel that one of the hallmarks of this disease complex is the absence of esophageal varices. It is clear from a review of the various authors that esophageal varices may in fact be present in the absence of portal vein hypertension, but that they are infrequent, usually not very prominent, and rarely the site of blood loss.

The causes of occlusion of the splenic vein are usually related to the proximity of the splenic vein to the pancreas, with chronic pancreatitis being the most frequent cause of occlusion and subsequent varices,<sup>8</sup> as was the case with the patient presented here. Gastroduodenal varices have also been reported secondary to malignancy in the tail of the pancreas.<sup>3,7</sup>

Clinically, there is no uniform presentation of patients with splenic vein occlusion. It may, in fact, remain an asymptomatic condition.<sup>10</sup> Presentation is most often secondary to blood loss from the varices, resulting either in chronic anemia or acute hemorrhage. Associated history may include symptoms caused by chronic pancreatitis or even malignancy of the pancreas. Findings may include splenomegaly, though the spleen is not always enlarged.<sup>4</sup> Hypersplenism has been reported secondary to occlusion of the splenic vein.<sup>7</sup>

Diagnosis of gastroduodenal varices involves the use of several modalities, including endoscopy, barium examination, angiography, and splenoportography.

Endoscopy might well identify the presence of varices, especially during an episode of active bleeding, but the definite identification of varices in the gastric fundus or duodenum can be very difficult, as this case illustrates.

Barium examination may be of significant help, though again definite identification of gastroduodenal varices can be extremely difficult. In our patient, gastric fundal varices could not be demonstrated, even in retrospect, and the duodenal changes were so non specific as to be of little help. Varices of the gastric fundus usually assume a smooth, lobulated, or polypoid pattern. These changes may be mistaken for a normal variation in the mucosal pattern, or, if identified as pathological, may be mistaken for polypoid gastric carcinoma, lymphosarcoma, polyps, Menetrier's disease, or intramural tumor.<sup>1,5,8</sup> Air contrast examination of the stomach may increase the likelihood of identifying gastric varices.

Angiographic evaluation should include injection into the celiac axis, which will demonstrate occlusion of the splenic vein, gastric varices, and a patent portal vein. Injection into the superior mesenteric artery, utilizing intraarterial Priscoline<sup>®</sup> prior to injection will usually confirm the absence of sig-

nificant esophageal varices, and will give even better visualization of the portal vein.

Splenoportography is most helpful, in that it will more clearly define the anatomy and more precisely outline the true extent of the varices,<sup>8,10</sup> which may include duodenal and esophageal components. Also, splenic pulp pressure may be measured at splenoportography and should reflect the hypertension in the splenic vein.

Armed with the knowledge that he will encounter venous hypertension, and with the anatomy defined by the splenoportogram, the surgeon is well prepared to avoid the problems which he might otherwise encounter. In the absence of a specific preoperative diagnosis, the presence of a normal liver, a large gastroepiploic vein, pancreatic inflammation, and splenomegaly at laparotomy should lead one to suspect splenic vein thrombosis.<sup>10</sup> If not recognized, gastrectomy or pyloroplasty would not only be ineffective but could well precipitate disastrous hemorrhage.<sup>9</sup>

Splenectomy is curative. Ligating the splenic artery first is helpful in reducing blood loss from the venous collaterals contained in the splenic ligaments. Though it was not attempted in the case reported here, consideration should be given to the possibility of embolizing the splenic artery via an arterial catheter, thus reducing splenic blood flow. Embolization of the splenic artery has been utilized to reduce splenic function in cases of hypersplenism.<sup>6</sup>

## SUMMARY

Gastroduodenal varices, in the absence of portal vein hypertension, may result in severe gastrointestinal blood loss. Chronic pancreatitis, resulting in splenic vein occlusion, is the most common cause of this situation, though it may rarely result from malignancy of the pancreas. Diagnostic tools include endoscopy, barium examination of the upper GI tract, angiography, measurement of the hepatic venous wedge pressure, and splenoportography. Splenectomy is curative.

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#### TOO MANY RUPTURED ANEURYSMS — Continued from Page 454

or 4 cm., and aneurysm may be present. If the patient has a pot belly, accurate physical examination may not be possible. If that patient has signs of arteriosclerosis such as a missing peripheral pulse, or coronary disease, he may well have aortic arteriosclerosis. A lateral abdominal film may reveal an aneurysm and is well worth ordering. If doubt exists, oblique films may show the curving lines of calcification which are suggestive. An untrasonogram or aortogram may be necessary for confirmation in questionable cases. When the diagnosis is made, the patient should be referred to a vascular surgeon for consultation. Some patients are in such poor condition, or so old that elective resection may not be undertaken but those patients are in the minority. It must be realized that their demise from ruptured aneurysms in the future is quite likely. By being alert to the problem of abdominal aortic aneurysms, it is my thought that physicians and

surgeons alike will miss the diagnosis less often so that the thirty-seven percent incidence of ruptured aneurysm at Eastern Maine Medical Center may be reduced to 20% or even 10% in the future with resulting benefit to our patients.

#### SUMMARY AND CONCLUSION

A case of a ruptured aneurysm in a patient under medical supervision is reported.

At Eastern Maine Medical Center over the past three years, there were fifty-seven resections for abdominal aortic aneurysm. In twenty-one of these cases, the aneurysm was ruptured.

By careful physical examination and by antero-posterior and lateral abdominal films in obese patients with arteriosclerosis, especially in patients over age 55, it would appear that more aneurysms will be discovered pre-rupture with resulting lower mortality and greatly decreased hospital expense.

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# Use of Balloon-Tipped (Swan-Ganz) Catheter in the Evaluation of a Pulmonary Arteriovenous Malformation\*

EDWARD M. HARROW, M.D., P. MAYNARD BEACH, M.D., JOE R. WISE, JR., M.D.,  
CHARLES LYNCH, M.D., WILLIAM G. B. GRAHAM, M.D. and GREGORY WIGHT

## ABSTRACT

A balloon-tipped catheter was used in the preoperative assessment of a patient with a solitary pulmonary arteriovenous fistula and coexistent chronic obstructive pulmonary disease and ischemic heart disease. Studies before and two months following surgical excision showed that the improvement in arterial oxygenation (49 mmHg vs 77 mmHg) and reduction in the fraction of the shunted cardiac output (37% vs 6%) closely approximated the predicted preoperative estimates.

## INTRODUCTION

Since their original description nearly seventy-five years ago<sup>1,2</sup> pulmonary arteriovenous malformations have become a recognized, though unusual cause of exercise intolerance and respiratory disability. With the development of modern diagnostic and surgical techniques, these anomalies have been diagnosed and corrected with increasing facility.<sup>3,4</sup> The patient described here had a large solitary pulmonary arteriovenous fistula, obstructive lung disease, and ischemic heart disease. The coincidence of these conditions complicated her clinical evaluation. By occluding the fistula with a balloon-tipped catheter, it was possible preoperatively to determine the degree of shunting and arterial hypoxemia cause by the malformation.

## CASE REPORT

E. H., a 51-year-old woman, was seen for evaluation of dyspnea and recurrent pulmonary infections. She denied symptoms of dyspnea until five years previously when she was hospitalized for an acute anterior myocardial infarction. Following her recovery, she complained of excessive fatigue and dyspnea on exertion such that she was unable to work. There was no family history of lung disease or congenital malformations, however, she did have a 40 pack-year smoking history.

She was a thin, mildly cachectic white female with BP 100/60, P 80, and R 20 which were unlabored. There were no hemangiomas or telangiectasias. The neck veins were not distended. A diffuse lift was palpable in the 5th ICS at the AAL. S<sub>1</sub> was normal and pulmonic valve closure was not increased. An S<sub>4</sub> gallop was audible at the left sternal border. Auscultation of the lungs revealed scattered wheezes and a systolic bruit at the base of the



Fig. 1. Chest laminogram showing a serpiginous retrocardiac density.

left lung. The extremities were symmetrically clubbed and mildly cyanotic. The patient was not polycythemic.

The EKG showed absent R waves in the right precordial leads consistent with an old anterior infarction. A retrocardiac density was present on the chest x-ray and tomograms suggested the presence of an A-V fistula in the left lower lobe (Figure 1). Right heart catheterization (Table 1) and pulmonary angiography (Figure 2) demonstrated a large solitary fistula originating from the vessels of the left anterior and medial bronchopulmonary segments. Coexistent fistulae in the opposite lung were excluded by a negative right sided arteriogram.

Pulmonary function studies showed a moderate obstructive impairment (Table 2). Arterial blood gases on room air and 100% oxygen demonstrated a resting PaO<sub>2</sub> of 49mmHg and a 37% right to left shunt. Exercise induced even greater hypoxemia and shunting, 43mmHg and 39% respectively. With balloon catheter occlusion of the proximal end of the fistula (Figure 3), the PaO<sub>2</sub> increased from 49 to 66mmHg and the shunt decreased from 37 to 8% (Table 3). A left heart catheterization with coronary arteriography showed a large diffuse ventricular aneurysm, 75% occlusion of the right coronary artery, nearly total occlusion of the left anterior descending artery and 50% occlusion of the left circumflex artery. A treadmill exercise test (Bruce) was negative. Because of the marked shunting with its resultant arterial hypoxemia and the considerable improvement that followed temporary fistula occlusion, the malformation was excised. Surgery was accomplished uneventfully by removal of the basal segments of the left lower lobe since the fistula was embedded well within the pulmonary parenchyma.

Two months postoperatively the patient was able to resume all but vigorous exercise. Studies at that time showed a PaO<sub>2</sub> of 77 mmHg and a right to left shunt of 6% (Table 3); values which were even better than predicted on the basis of preoperative fistula occlusion.

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TABLE 1

RIGHT HEART CATHETERIZATION		
Catheter Position	Pressure (mmHg)	
	Phasic	Mean
Right atrium		3
Right Ventricle	25/ 4	
Pulmonary artery	22/13	15
Wedge — pulmonary artery		8
Wedge — fistula		10

### DISCUSSION

Pulmonary arteriovenous fistulas can be either solitary or multiple and are often associated with other vascular anomalies.<sup>5</sup> Hereditary hemorrhagic telangiectasia is reported to coexist in 60% of these patients.<sup>6</sup> When clinically significant, pulmonary A-V malformations are often associated with the triad of cyanosis, exertional dyspnea and digital clubbing.<sup>7</sup>

The severity of the respiratory symptoms caused by pulmonary A-V malformations can be correlated with their radiographic size, which is presumably an index of the degree of shunting through the abnormal vessel.<sup>8</sup> The use of the Swan-Ganz catheter, however, allowed selective fistula occlusion and, therefore, enabled calculation of the actual degree of shunting through the malformation itself.

Significant pulmonary arteriovenous shunting without arteriographically demonstrable fistulae has been reported in patients with obstructive pulmo-

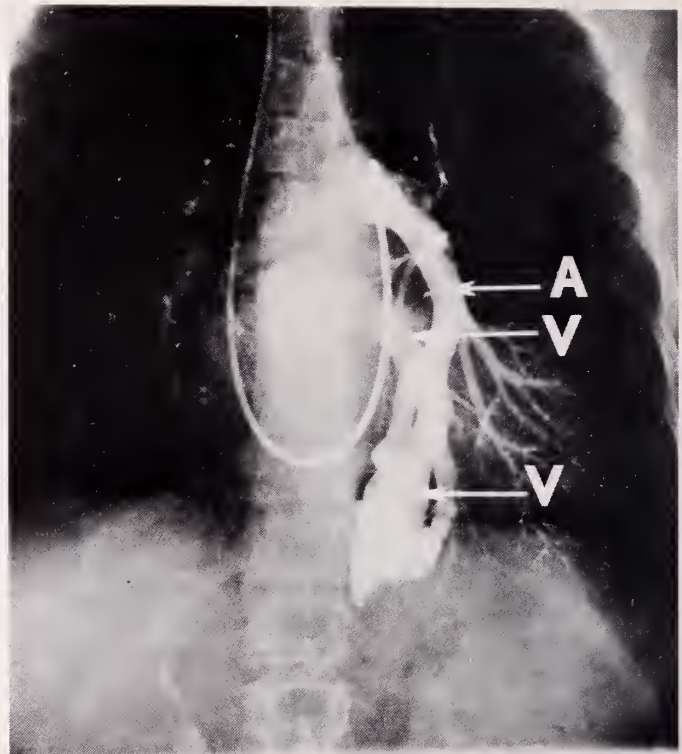


Fig. 2. Arterial phase of left main pulmonary artery injection, showing filling of pulmonary artery branch (A) to left lower lobe, with shunting through arteriovenous malformation to large draining vein (V). (Reprinted with permission of the editors of *Chest*.)

TABLE 2

VENTILATORY DYNAMICS					
	Predicted	Before Bronchodilators		After Bronchodilators	
		Observed	% Predicted	Observed	% Predicted
FEV1 (L)	1.92	0.82	43	1.07	56
FVC (L)	2.54	1.45	57	1.75	71
FEV1/FVC (%)	75	57		61	
MVV (L)	62	45	72	44	71

nary disease.<sup>9</sup> In view of the coexistent chronic obstructive pulmonary disease in this patient, quantitation of the shunt through the fistula was made to define the degree to which it alone was responsible for the patient's arterial hypoxemia. The fall in the right to left shunt to near normal levels during balloon catheter occlusion demonstrated that the fistula was primarily responsible for the patient's hypoxemia. In addition, it also confirmed the angiographic findings that only a single fistula was present.

The data obtained preoperatively in this patient provided an accurate assessment of the improved arterial oxygenation and hemodynamics that would result upon fistula excision. Comparison of these data with the postoperative result showed that the rise in PaO<sub>2</sub> (66mmHg vs 77mmHg) and fall in shunt fraction (8% vs 6%) was in fact better than initially anticipated. These discrepancies may be due either

to the patient's not smoking for two months prior to the follow-up study and/or the possibility that fistula occlusion at the time of the catheterization was not complete.

It appears that preoperative occlusion of pulmonary arteriovenous malformations can provide an accurate estimation of the postoperative physiologic results.

### ACKNOWLEDGMENT

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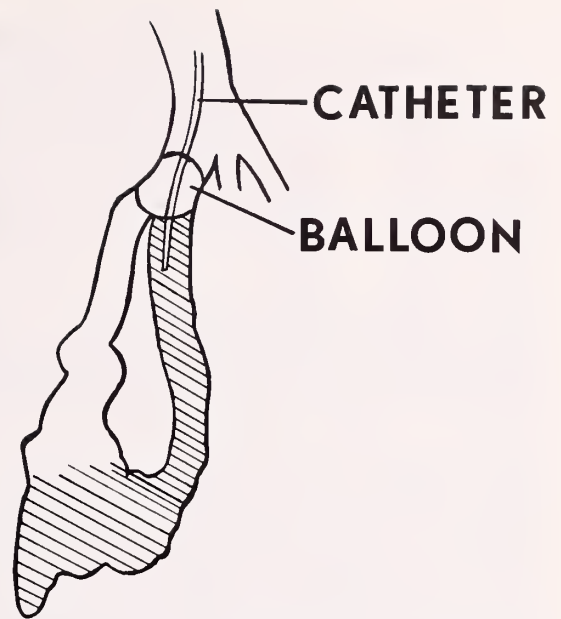
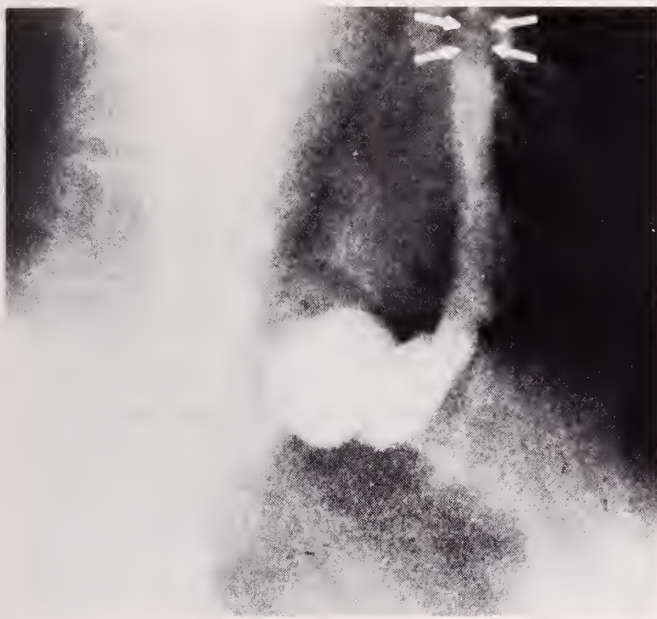


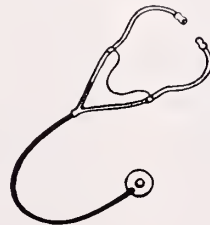
Fig. 3

Left: Single frame from 35mm cine, showing partially opacified arteriovenous malformation and occluding Swan-Ganz balloon (arrows).  
 Right: Diagrammatic illustration of cine frame showing balloon occlusion just above the bifurcation of the fistula with catheter tip in the lateral limb which is opacified (shaded area). (Reprinted with permission of the editors of *Chest*.)

**TABLE 3**  
**ARTERIAL BLOOD GASES ON ROOM AIR AND 100% O<sub>2</sub>**

	<i>Fistula Open</i>		<i>Fistula Closed</i>	
	<i>Preoperatively</i>	<i>Exercise</i>	<i>Preoperatively</i>	<i>Postoperatively</i>
	<i>Rest</i>		<i>Rest</i>	<i>Rest</i>
Room Air:				
pH	7.46	7.43	7.43	7.45
PaCO <sub>2</sub> (mmHg)	33	33	31	33
O <sub>2</sub> sat(%)	87	80	94	96
PaO <sub>2</sub> (mmHg)	49	43	66	77
100% O <sub>2</sub> :				
pH	7.43	7.42	7.45	7.47
PaCO <sub>2</sub> (mmHg)	30	29	27	28
O <sub>2</sub> sat(%)	96	94	100	100
PaO <sub>2</sub> (mmHg)	75	65	552	557
Shunt (%):	37	39	9	6

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# Review of Surgery

Staff Paper Prepared for the National  
Professional Standards Review Council

SHARMAN K. STEPHENS AND JAMES I. CLEEMAN, M.D.\*

## STATEMENT OF THE PROBLEM

Over the past several years, concerns over increasing public and private expenditures for health care have led to examinations of various aspects affecting the quality and cost of health care in the United States. One of these aspects receiving substantial attention and causing considerable controversy is "unnecessary surgery." To date, however, there is no agreed upon definition for "necessary" or "unnecessary" surgery.

A frequently cited categorization of operations that might be termed "unnecessary" comes from the Study on Surgical Services for the United States (SOSSUS) (See Table 1). The Study Report qualifies the categorization by saying that "careful study of each case is essential before a judgment can be made as to degree of necessity."<sup>1</sup> The Report notes that necessity for a procedure can be medical, personal, or social. Dr. Larry C. Carey (Ohio State University) prefers to define necessary surgery as that which is "lifesaving, life prolonging or quality-of-life improving."<sup>2</sup> The last of the three is most difficult to interpret. An alternative approach has been suggested by Dr. George Crile, Jr. (Cleveland Clinic). Dr. Crile recommends that the word "inappropriate" be used rather than "unnecessary," since operations to correct other than life-threatening conditions cannot be called necessary. Dr. Crile goes on to define "inappropriate" as implying that: "1) a surgical operation was not the best way to treat the disease; 2) the type of operation used was not the best way to treat the individual patient; or 3) the surgeon who did the operation was not trained or experienced enough to do the operation safely and well."<sup>3</sup>

The above attempts to define "unnecessary" surgery are not provided as recommendations, but rather as illustrations of the "state of the art." An overview article in the May 3, 1976, issue of *Medical World News* reflects what now appears to be a common opinion about the role that the definition of "unnecessary surgery" plays.

"The debate over unnecessary surgery will not be settled until a clearer definition of the term is agreed upon. This will require that the indications for procedures be drawn with more precision than they are now. For the present, there remains no

TABLE 1

### CATEGORIES OF POTENTIAL UNNECESSARY OPERATIONS\*

1. Operations where no pathologic tissue is removed.
2. Operations whose indications are a matter of judgment.
3. Operations to alleviate enduring or tolerable symptoms.
4. Discretionary operations for asymptomatic, nonpathologic, nonthreatening disorders.
5. Operations now outdated, obsolete, or discredited.

\*Careful study of each case is essential before a judgment can be made as to degree of necessity.

Source: *Surgery in the United States: A Summary Report of the Study on Surgical Services for the United States*, pp. 89-90.

Note: A sixth category is shown in the Subcommittee on Oversight and Investigations of the Committee on Interstate and Foreign Commerce Report, "Cost and Quality of Health Care: Unnecessary Surgery." The Report cites Dr. George Zuidema (Chairman of the Executive Committee of the SOSSUS) as presenting in testimony the following additional sixth category (p. 9):

6. Operations done primarily for the personal gain of the surgeon, wherein the weight of informed opinion would deny any indication to the present.

generally acceptable means of assessing what percentage of operations is necessary."<sup>4</sup>

Despite the limitation imposed by a lack of definition, discussions and debates on unnecessary surgery are taking place. Basically there are four categories of studies that are used to demonstrate the existence of unnecessary surgery:

- Variations in rates of surgery among different localities,
- Variations in rates of surgery between fee-for-service and prepaid delivery systems,
- Second opinions for surgery, and
- Chart review by preset criteria.

A brief discussion on the findings and limitations of each of these four categories follows.

## VARIATIONS IN RATES OF SURGERY AMONG DIFFERENT LOCALITIES

The largest body of data related to unnecessary surgery is that on variations in surgical rates. One of the earliest studies reporting variation in the rate of surgery was conducted in 1952. Lembcke, studying the incidence of appendectomies in 23 hospital service areas in and around Rochester, N.Y., found a range from 25 to 69 operations per 10,000 population. No correlation between low appendectomy rates and high mortality rates from appendicitis could be found. Lembcke assumed that a "reasonable inference" would be that accessibility to physi-

\*Health Standards and Quality Bureau, Division of Peer Review, Health Care Financing Administration, 5600 Fishers Lane, Rockville, MD.

TABLE 2

RATES PER 100,000 POPULATION FOR INPATIENTS DISCHARGED FROM SHORT-STAY HOSPITALS BY SURGICAL CATEGORY, GEOGRAPHIC REGION, AND DATE\*

Surgical Category	ICDA	United States				Northeast	North Central	South	West
		1971	1973	1974	1975	1975	1975	1975	1975
Tonsillectomy	21.1-21.2	478.3	429.7	389.8	327.8	274.7	401.1	295.2	344.0
Repair of Inguinal Hernia	38.2-38.3	241.5	255.3	252.7	262.6	294.2	302.9	217.7	240.1
Appendectomy <sup>1</sup>	41.1	157.3	164.5	155.0	152.5	127.7	170.8	152.8	156.4
Cholecystectomy	43.5	184.6	199.8	193.8	211.4	232.2	239.9	191.2	176.7
Hemorrhoidectomy	51.3	105.4	106.0	112.8	96.3	93.7	101.8	103.8	77.9
Mastectomy	65.2-65.6	125.7	140.8	161.8	162.5	176.6	182.7	152.2	131.5
Hysterectomy	69.1-69.5	282.0	335.2	335.2	346.9	266.7	348.8	389.1	374.0

\*Taken from *Surgical Operations in Short-Stay Hospitals*, 1971 and 1973 and *Utilization of Short-Stay Hospitals: Annual Summary for the United States*, 1974 and 1975, compiled by the National Center for Health Statistics.

<sup>1</sup>Limited to estimated number of appendectomies excluding those performed incidental to other abdominal surgery.

cians and hospitals was the more important factor in determining appendectomy rates.<sup>5</sup>

In a similar vein, studies by Lewis in Kansas and by Wennberg and Gittelsohn in Vermont and Maine showed great regional variations for a number of common procedures (tonsillectomy, appendectomy, hemorrhoidectomy, cholecystectomy, varicose vein).<sup>6,7,8</sup> Following are examples of the variations found:

- Tonsillectomy — from 153.4 to 432.6/10,000 pop. (Kansas)
- Hysterectomy — from 20 to 60/10,000 pop. (Vermont)
- Cholecystectomy — from 27 to 55/10,000 pop. (Maine)

The studies found a correlation between the higher rates of surgery and the number of surgeons and facilities.

A study by Bunker comparing operations and surgeons in the United States to those in England and Wales found that, per capita, the United States has twice as many surgeons as England and Wales and twice the number of operations per 100,000 population.<sup>9</sup>

Gornick demonstrated, for 1971, the variations in the percentage of Medicare patients discharged after surgery. The range was from a low in the South of 25.3 percent of discharges to a high in the Northeast of 34.1 percent.<sup>10</sup> Table 2 is a chart showing variations in surgical rates over time and among regions of the United States.

The SOSSUS Report, previously mentioned, studied operations in four areas in three geographic regions. This study found a variation from 58 to 91 operations per 1,000 persons. This Report supports the correlation found in the earlier studies between high surgical rates and the high number of physicians doing surgery.<sup>11</sup>

There is a major limitation, however, in using the variation in surgical rates as a definite indication of unnecessary surgery. Since there are currently no guidelines for determining which of the surgical rates are the most appropriate, could not, in fact, the higher rates represent the meeting of previously unmet needs for surgery? It can be argued that,

since the areas with lower rates of surgery do not appear to have significantly higher mortality statistics than the areas with higher surgical rates, the higher rates represent unneeded surgery. However, as was previously noted by Crile, the mortality statistics argument can be countered because so few of the operations are actually a matter of life or death. Data appear to show relationships between rates of surgery and both availability of physicians performing surgery and hospital beds. Nevertheless, the absence of standards for surgical rates precludes knowing whether the higher or lower rates are the more appropriate.

#### VARIATION IN RATES OF SURGERY BETWEEN FEE-FOR-SERVICE AND PREPAID DELIVERY SYSTEMS

Another frequently cited indicator of unnecessary surgery is the difference in surgical rates between similar populations — a portion receiving health care under a prepaid financial arrangement and the remainder under a fee-for-service system. The most frequently cited study illustrating this phenomenon is of the Federal Employees Health Benefits Program.<sup>12</sup> For 1968, the following inpatient surgery rates were found:

Surgical Procedures	Rate per 1,000	
	Fee for Service	Prepaid
All Procedures	75	34
Tonsillectomy and/or Adenoidectomy	6.9	2.4
Female Surgery	9.2	4.8
Appendectomy	2.1	1.1
Cholecystectomy	2.1	1.5

As part of its continuing work in studying the Federal Employees Health Benefits Program, the National Center for Health Services Research is currently doing an in-depth examination to compare the inpatient surgical practices in fee-for-service vs. group practice settings.

Another frequently mentioned study is that of Gaus, et al., "Contrast in HMO and Fee-for-Service Performance." This study, reported in the *Social Security Bulletin*, compares various aspects of HMO performance with those of the fee-for-service system for the Medicaid population. The surgical

rates in the group-practice plans were half those of the fee-for-service. The more interesting finding of this study was that the capitation payment alone did not appear to be the major reason for the difference in utilization. The study suggests, rather, that it is the organized group practice aspect that is significant.<sup>13</sup>

In contrast to these two studies is one reported by Perkoff, et al., in which a difference in surgical rates between prepaid and fee-for-service groups was not found. The explanation proposed for this "lack of effect" was that there was generally a high level of quality surgical care in the study area.<sup>14</sup>

Although one possible explanation for the lower surgical rates observed in prepaid group practice is that the absence of a financial incentive for the physician-surgeon to overutilize reduces the amount of "unnecessary surgery" performed, a counter-explanation can be offered: that the prepaid system might be denying some patients surgery that is appropriate.<sup>15</sup> As was noted in the previous section on geographic variation in rates of surgery, the use of variation data alone as a definite indicator of "unnecessary surgery" is precluded by the absence of a definition of what the appropriate or correct rates of surgery are.

#### SECOND OPINION FOR SURGERY

The third set of data, one of the most controversial, is the result of a study on the presurgical programs established by the United Storeworkers Union and by District Council 37 of the American Federation of State, County and Municipal Employees. The initial results of this continuing study were reported by McCarthy and Widmer in December 1974, in "Effects of Screening by Consultants on Recommended Elective Surgical Procedures." The study found that in the voluntary second opinion program 30.4 percent of the operations were not confirmed by the consultation, and in the mandatory program 17.6 percent were not confirmed.<sup>16</sup> Because of the bias felt to exist in selection of patients for the voluntary program, it is the 17 percent figure that has received the greater attention. Specifically, it was this 17 percent figure that was used by the Subcommittee on Oversight and Investigations of the Committee on Interstate and Foreign Commerce to extrapolate a figure of 2,380,000 unnecessary surgeries performed in 1975.<sup>17</sup>

Since the publication of the Subcommittee's Report in which these data were represented, a great deal has been written about the methodological problems in using Dr. McCarthy's data to develop figures for unnecessary surgery.<sup>18,19,20,21</sup> In summary, the following reasons are the most frequently cited against performing the extrapolation:

- 1) Researchers themselves cautioned against applying results to the general population;
- 2) Most of the procedures involved were dis-

cretionary. Non-confirmation by the second opinion consultant simply represents a difference of opinion between two physicians (i.e., there is no absolute way to know whether the second opinion is the correct one);

- 3) Use of the 17 percent figure does not take into account surgery that is eventually performed, i.e., deferred surgery.

In regard to this last argument, more recent reports from the study reveal that 32.4 percent of the non-confirmed surgeries in the mandatory program were performed at a later date.

Dr. McCarthy has also found that a surprisingly high percentage (voluntary — 29.4%, mandatory — 11.7%) of patients were confirmed for surgery but elected not to have it. Obviously, deferring warranted surgery can mean further disability and possibly premature death for the patient. Another finding from the more recent analyses is that surgical claims after the program was initiated were nine percent lower than before, while national claims have increased approximately 20 percent. This "sentinel effect" occurred as patients and physicians became aware of the second opinion program.<sup>44</sup>

Over the next several years, second opinion programs will be increasing. Several of the Blue Shield Plans have initiated such programs, including one started in January 1976, by Blue Cross/Blue Shield of Greater New York. A survey of second opinion programs performed for HEW found that, as of early 1977, there were about seventeen programs either operational or about to become so.<sup>23</sup> The Department, under the authority of Section 222 of the Social Security Act, is planning to undertake a demonstration program in second surgical opinion. The primary objective of the experiment is to test whether coverage of optional opinions for elective surgery will produce net cost savings for the Medicare and Medicaid programs without adversely affecting the quality of care provided to beneficiaries.

#### CHART REVIEW BY PRESET CRITERIA

The final category of data used to demonstrate the existence and extent of unnecessary surgery are the results of reviews of patient charts.

Frederick's review of the literature identified 11 such reports dating from 1946.<sup>24</sup> Generally the studies are on a specific procedure, e.g., hysterectomy, tonsillectomy. In some of the studies preset criteria are used. In others the approach is review by specialists.

The conclusion of one of the earliest studies was that 39 percent of the hysterectomy procedures should not have been done.

This study by Dr. Doyle was followed by three others, two of which upheld his findings.<sup>25</sup>

The more recent studies in this category involve the use of preset criteria for several common surgical procedures. The studies reported by Emerson

involve 12 hospitals and 833 operations in the first case, and 28 hospitals and 4,929 operations in the second. Both studies found less than one percent of the surgery was unjustified. It is important to note that the researcher qualifies his one percent finding with the fact that the hospitals "had strong medical care evaluation programs."<sup>26,27</sup> An expansion of this study, using similar methodology and involving the State of New York, is apparently in the planning stages.<sup>28</sup>

Chart review by preset criteria is attractive because the methodology itself entails establishing guidelines and definitions as to what is to be considered unnecessary. However, there is a major limitation to this type of study. Variations in the "tightness" of the criteria and in the stringency with which they are applied can result in different findings.

### MEDICAL NECESSITY PROJECT

Although not used to indicate unnecessary surgery, the recently announced project by Blue Cross/Blue Shield to withhold routine payment for certain diagnostic and surgical procedures is of interest. Written justification by the physician will have to be made before payment will be authorized. The list was developed through consultation with a number of medical specialty groups and health care professional organizations.

"The procedures were identified because each fits into one of four specific categories:

- New procedures of unproven value;
- Established procedures of questionable current usefulness;
- Procedures which tend to be redundant when performed in combination with other procedures; and
- Diagnostic procedures which are unlikely to provide a physician with additional information when they are repeated again and again."<sup>29</sup>

### STATEMENT OF THE PROBLEM: SUMMARY

As has been discussed, all of the methods used to substantiate the existence and extent of unnecessary surgery have limitations. Variations in surgical rates can be demonstrated and a statistical relationship to the availability of physicians and facilities can be drawn. Special chart review studies have found varying amounts of unnecessary surgery. However, the most accurate statement of the problem appears to be that unnecessary surgery exists, but its true scope is yet to be determined.

The current state of affairs, in which there is 1) disagreement over definitions for the terms "unnecessary" and "necessary" surgery, 2) disagreement on interpreting the variations in surgical rates, and 3) disagreement on interpreting a consultant's non-concurrence regarding the advisability of surgery for an individual, is expected to persist for

awhile. This situation is not that surprising, since as in so many other things related to medicine the lack of a data base for outcomes (mortality and disability) of medical intervention precludes definitive determinations of the "preferred" courses of treatment. Because of the difficulty and cost of performing controlled clinical trials on all procedures, the absence of an adequate outcomes data base will likely remain for some time. Thus, controversy over "unnecessary surgery" will continue.

In the absence of information from which to draw definitive conclusions, the existence of disagreement is not necessarily a bad thing. What becomes important is how, recognizing the state of divergence of opinion, questions of medical necessity for surgery are dealt with.

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## Management of Hypothyroidism

WILLIAM E. COBB, M.D. and IVOR M. D. JACKSON, M.D.

### ABSTRACT

Most causes of primary, secondary, and tertiary hypothyroidism require lifelong thyroid hormone replacement. Early recognition and treatment is of particular importance for neonates in order to prevent mental retardation. Sodium levothyroxine is the preferred agent because of consistent potency, restoration of normal, constant serum levels of T<sub>4</sub> and T<sub>3</sub>, and ease of interpretation of thyroid hormone levels. Other agents, because they contain T<sub>3</sub>, result in post-absorptive elevated T<sub>3</sub> serum concentrations that may cause thyrotoxic symptoms and reduction of T<sub>4</sub> levels. This, in turn, may give rise to misleading estimates of thyroid dosage. Low initial dosage is indicated in older patients, especially those with heart disease or long duration of hypothyroidism. The exception is myxedema coma where large intravenous doses may reduce mortality despite an increased risk of cardiovascular complications. Corticosteroids are indicated whenever ACTH or primary adrenal insufficiency coexists, with hypothyroidism. Maintenance doses of thyroid hormone are those which just suppress TSH into the normal range. Restoration of a normal hypothalamic-pituitary-thyroid axis occurs generally by 6 weeks after stopping thyroid medication in euthyroid subjects. The need for replacement can be assessed using TSH and thyroid hormone levels. Patients with the sick euthyroid or low T<sub>3</sub> syndromes are not candidates for thyroid hormone therapy.

Hypothyroidism due to deficient thyroid hormone production may result from an abnormality of the thyroid gland itself (primary hypothyroidism) or from deficiencies of thyroid stimulating hormone (secondary hypothyroidism) or thyrotropin releasing hormone (tertiary hypothyroidism) in the presence of a normal thyroid gland.<sup>1</sup>

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Rarely, tissue resistance to the action of thyroid hormone<sup>2</sup> or thyroid gland resistance to thyroid stimulating hormone produces signs of insufficiency. Mental retardation (irreversible if not treated in early infancy), growth retardation, and altered sexual maturation in childhood, as well as accelerated development of atherosclerosis in adults, are potentially devastating consequences of untreated hypothyroidism.

In 1891, some 18 years after Gull's original description of hypothyroidism, Murray administered injections of sheep thyroid extract to myxedematous subjects, thereby establishing hormone replacement as the basis for management of thyroid insufficiency.<sup>3</sup> A variety of preparations for oral and parenteral use are now available, but synthetic sodium levothyroxine is superior to other agents for long-term replacement therapy. Sensitive radioimmunoassays for triiodothyronine (T<sub>3</sub>), thyroxine (tetraiodothyronine) (T<sub>4</sub>), and thyrotropin (thyrotropin) (TSH) and synthesis of the hypothalamic tripeptide, thyrotropin-releasing hormone (TRH), are recent developments which have contributed to greater understanding of abnormal thyroid physiology and improved methods for assessing thyroid hormone dosage.<sup>4-9</sup>

### THERAPEUTIC USE OF THYROID PERPARATIONS (Table 1)

#### *Levothyroxine Sodium*

Sodium levothyroxine is the drug of choice for the long-term management of hypothyroidism. Earlier objection to its use was based on the belief that T<sub>3</sub>, which is more potent than T<sub>4</sub>, was derived predominantly from thyroidal secretion, and that T<sub>3</sub> deficiency might occur if thyroxine alone was prescribed.<sup>10</sup> It is now known that much of the circulating T<sub>4</sub> is converted to T<sub>3</sub> by peripheral tissues, suggesting an important role for T<sub>4</sub> as a prohormone.<sup>11</sup> A single daily oral dose of T<sub>4</sub> results in constant blood levels of T<sub>4</sub> and T<sub>3</sub> throughout the day, thereby mimicking thyroid hormone levels seen in normal subjects.<sup>4</sup> This is attributable to the long elimination half-life of T<sub>4</sub> (7 days) and a relatively constant rate of conversion of T<sub>4</sub> to T<sub>3</sub>.<sup>12,13</sup>

About 50% of an administered dose of levothyroxine is absorbed from the gastrointestinal tract, although some patients absorb it poorly and require higher doses.<sup>14</sup> Malabsorption syndromes, cholest-

TABLE 1

AVAILABLE PREPARATIONS, USUAL MAINTENANCE DOSAGE, AND THYROID HORMONE LEVELS DURING MAINTENANCE THERAPY					
Preparation	Composition	Tablet Strengths	Maintenance Dose	Serum Hormone Levels	
				T <sub>4</sub>	T <sub>3</sub>
Levothyroxine Sodium	T <sub>4</sub>	0.025, 0.05, 0.1, 0.15, 0.2, 0.3, and 0.5 mg <sup>a</sup>	0.1-0.2 mg daily or 1-2 mg weekly	normal	normal
Liothyronine (Levo-triiodothyronine) Sodium	T <sub>3</sub>	5, 25 and 50 µg <sup>b</sup>	25 µg two or three times daily	low	elevated
Thyroid USP	20-35 µg T <sub>4</sub> and 8-14 µg T <sub>3</sub> <sup>c</sup> per 60 mg (1 grain)	15, 30, 60, 90, 120, 180, 240, 300 mg	90-180 mg daily	low normal	usually elevated
Thyroglobulin	20-35 µg T <sub>4</sub> and 11-21 µg T <sub>3</sub> per 60 mg (1 grain)	15, 30, 60, 90, 180, and 300 mg	90-180 mg daily	low normal	usually elevated
Liotrix	Euthyroid: 60 µg T <sub>4</sub> and 15 µg T <sub>3</sub> . Thyrolar: 50 µg T <sub>4</sub> 12.5 µg T <sub>3</sub> .	½, 1, 2, and 3 "grain equivalents"	1.5-3.0 "grain equivalents"	low normal	often elevated

<sup>a</sup>: Parenteral preparation: Lyophilized powder 0.5 mg, with mannitol 10 mg and 5 ml normal saline as diluent.

<sup>b</sup>: Parenteral preparation: Powder (for solution) 114 µg/ml; not commercially available but Smith Kline & French Laboratories will supply kit upon request for use in myxedema.

<sup>c</sup>: Range of T<sub>4</sub>:T<sub>3</sub> ratio is 2-3:1 for pig glands and 3-4.5:1 for beef or sheep glands.

tyramine administration,<sup>15</sup> and ingestion of soybean formula,<sup>16</sup> may interfere with thyroxine absorption.

**Initiation of treatment.** Three factors must be considered in the selection of a starting dose: (1) patients age, (2) duration and severity of hypothyroidism, and (3) associated disease. In the neonate, early and aggressive therapy is imperative because mental retardation may be prevented by rapid restoration of the euthyroid state (see section on neonatal hypothyroidism, below). Older children and young adults are generally started on the approximate maintenance or half-maintenance dosage of 0.05 to 0.2 mg daily, particularly if the hypothyroidism is mild and of short duration. Older patients are presumed to have coronary artery disease, whether clinically manifest or not, and here the initial dose is much lower, in the range of 12.5 to 50 µg daily.

**Dose adjustments.** Achievement of steady-state T<sub>4</sub> concentrations will be about 95% complete after approximately 35 days, based on an elimination half-life for sodium levothyroxine of 7 days. Thus, the interval between dose adjustments should probably be at least one month in most cases. For patients with proven or suspected coronary artery disease, each increment should be no greater than the original starting dose, because small changes may have dramatic effects on the frequency and severity of angina, congestive heart failure, and cardiac arrhythmias.

**Maintenance dose.** The optimal maintenance dose precisely re-establishes premorbid T<sub>4</sub> and T<sub>3</sub> concentrations. In normal individuals, thyroid hormone concentrations remain remarkably constant throughout the day. In hypothyroid subjects a critical concentration of serum thyroxine exists, beyond which small increases in thyroid hormone dosage

markedly suppress TSH and the TSH response to intravenous TRH.<sup>17</sup> This implies extremely sensitive regulation of the hypothalamic-pituitary-thyroid axis and suggests that an ideal thyroid hormone concentration exists for each patient.

Older approaches to identifying this optimal level, including normalization of serum cholesterol, creatinine phosphokinase, basal metabolic rate and deep tendon reflexes, are crude and insensitive.<sup>18</sup> Left ventricular performance, as measured by the degree of prolongation of the pre-ejection period, has been shown to be a sensitive (although indirect) index of peripheral thyroid hormone action.<sup>19</sup> Further study of erythrocyte carbonic anhydrase activity<sup>20</sup> and sodium or zinc concentrations<sup>21</sup> may subsequently establish their value for assessing an endpoint in thyroid hormone replacement. Thyroid hormone measurements themselves indicate hormone concentration but not end-organ function.

In primary hypothyroidism, return of an elevated TSH to normal is the most sensitive single indicator of adequate thyroid hormone replacement.<sup>7,8</sup> One method for determining the optimal maintenance dose of sodium levothyroxine is to adjust dosage until TSH levels are just suppressed into the normal range. Even greater precision is possible by measuring the TSH response to TRH stimulation, but the procedure is time-consuming, expensive, and its role in routine dosage selection remains to be established.<sup>22</sup> Application of these methods has substantially reduced recommended doses of sodium levothyroxine below those previously advocated.<sup>23-25</sup> Less than 0.2 mg daily is appropriate for 90% of patients,<sup>24</sup> with 0.1 to 0.15 mg daily being sufficient in most.<sup>25</sup> Patients receiving 0.3 mg daily, although appearing euthyroid, demonstrate meta-

bolic alterations and abnormalities of iodothyronine kinetics suggestive of subclinical hyperthyroidism.<sup>26</sup> Since requirements may depend on body size and absorption, every patient must be individually assessed.

Reduced dosage and maintenance of relative hypothyroidism may be necessary in some patients (eg, those with severe coronary artery obstruction) to prevent exacerbation of their underlying disease. When compliance is poor, a single dose of 2.0 mg or less weekly may be given.<sup>27</sup>

Although a return to normal of TSH and the TSH response to TRH may be used to approximate optimally thyroid hormone replacement, the TSH radioimmunoassay is insensitive at normal or low levels of TSH and is not helpful in identifying those patients receiving excessive doses of thyroid hormone. In secondary and tertiary hypothyroidism, the TSH may be normal or low prior to treatment and cannot, therefore, be used to optimize replacement. These are circumstances where serum thyroid hormone levels are of particular value in assessing dosage.

Serum T4 and T3 should both fall within the normal range in optimally treated patients. Early reports of high T4 levels on sodium levothyroxine<sup>24,28,29</sup> resulted, in part, from lack of knowledge of peripheral T4 to T3 conversion\* and probably reflect the use of excessive replacement doses.<sup>24,25</sup> In some instances an elevated T3 level with normal T4 ("T3 thyrotoxicosis") may be the only evidence of levothyroxine overdosage,<sup>30,31</sup> suggesting that measurement of both hormones is required to correctly assess dosage. An elevation of either T4 or T3 (or both) requires a downward adjustment of levothyroxine dosage. During pregnancy, sex hormone therapy, or other conditions altering thyroid-binding proteins, measurement of free hormone levels, thyroid binding globulin or T3 resin uptake is required for proper interpretation of results.<sup>32</sup>

### Thyroid USP (Desiccated Thyroid)

This crude powder contains a mixture of iodinated proteins, tyrosines, and thyronines made by drying defatted thyroid glands of beef, pigs or sheep. Variable potency has been<sup>33</sup> and continues to be<sup>34</sup> a problem, since the standard set by the United States Pharmacopeia is based on total iodine content (0.17 to 0.23 percent) rather than biological assay. (Some companies, such as Armour, perform bioassays to assure uniform potency in every batch). Thyroid glands of different animals have different T4:T3 ratios (range, 2-5:1 by weight) and varying absolute quantities of each hormone.<sup>35</sup> This makes it difficult, if not impossible, to establish equivalent dosages with synthetic thyroid hormone preparations. In

\* Since T3 was thought to derive solely from thyroid gland secretion and was known to have greater activity, a higher T4 concentration was believed to be important.

## Tablets Percodan® II

**DESCRIPTION** Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (WARNING: May be habit forming), 0.38 mg. oxycodone terephthalate (WARNING: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

**INDICATIONS** For the relief of moderate to moderately severe pain.

**CONTRAINDICATIONS** Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

**WARNINGS Drug Dependence** Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

**Usage in ambulatory patients** Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

**Interaction with other central nervous system depressants** Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

**Usage in pregnancy** Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

**Usage in children** PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

**PRECAUTIONS Head injury and increased intracranial pressure** The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

**Acute abdominal conditions** The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

**Special risk patients** PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

**ADVERSE REACTIONS** The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

**DOSAGE AND ADMINISTRATION** Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

**DRUG INTERACTIONS** The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

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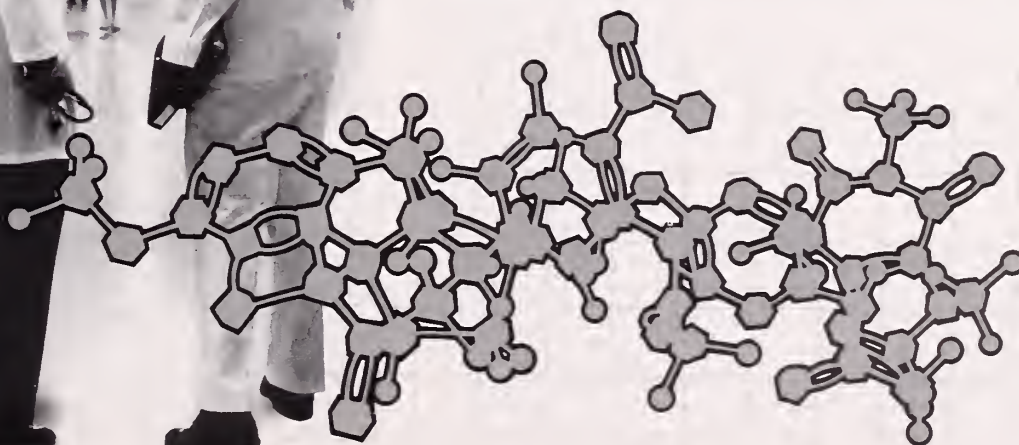
## Effective relief of moderate to moderately severe pain

Tablets

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each yellow, scored tablet contains: 4.50 mg oxycodone HCl (WARNING: may be habit forming), 0.38 mg oxycodone terephthalate (WARNING: may be habit forming), 224 mg aspirin, 160 mg phenacetin, 32 mg caffeine

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II



most instances 60 mg (1 grain) of thyroid is the equivalent, or less, of 0.1 mg sodium levothyroxine. Thus, the recommended full replacement dose of USP Thyroid® is 90-180 mg. daily. As with sodium thyroxine, treatment is initiated with low doses, eg, 15-30 mg.

Truly equipotent preparations of desiccated thyroid are as effective as sodium levothyroxine in treating hypothyroidism,<sup>36</sup> but the incidence of hyperthyroid-like side effects is increased<sup>31</sup> due to a postabsorptive rise in T3 to an abnormally high level.<sup>4</sup> In contrast, the T4 concentration remains constant and in the low normal range over a wide range of thyroid dosage, whether or not symptoms of thyroid hormone excess are present.<sup>31</sup> Thus, unlike sodium levothyroxine, the use of thyroid USP results in thyroid hormone concentrations that cannot be used to assess dosage.

#### *Thyroglobulin*

Thyroglobulin (Prolid®) is an extract of pig thyroid that is subjected to greater purification than desiccated thyroid and is standardized by a bioassay. It is more expensive than desiccated thyroid. Since thyroglobulin contains T4 and T3 in a ratio of 2.5:1, occasional thyrotoxic symptoms and high T3 and low normal T4 levels are to be expected.

#### *Liotrix*

Combinations of synthetic T4 and T3, in a ratio of 4:1, were marketed chiefly to provide a thyroid preparation that would mimic the proportion of T4 and T3 found in human thyroid glands.<sup>35</sup> This ratio has subsequently been shown to approximate 20:1.<sup>37</sup> Although its effectiveness has been well demonstrated, most patients express a preference for sodium levothyroxine because of thyrotoxic symptoms experienced on liotrix.<sup>38</sup> The mechanism for these adverse effects, like that of desiccated thyroid, involves a postabsorptive T3 rise. This stems from the relatively high content of T3 and its more complete absorption and shorter half-life, as compared to T4.

One liotrix preparation (Thyrolar®) contains 60 µg levothyroxine sodium and 15 µg liothyronine (L-triiodothyronine), while another (Euthroid®) contains 50 µg and 12.5 µg, respectively. Despite the different amounts of hormones, both Thyrolar and Euthroid are labelled "1 grain equivalent." The maintenance dose, like that for desiccated thyroid, is 1.5 to 3.0 grains ("grain equivalents") daily.

#### *Liothyronine (L-triiodothyronine) Sodium*

This hormone is 3 to 4 times as potent as sodium levothyroxine in restoring hypothyroid patients to a normal metabolic state and is nearly completely absorbed when given orally.<sup>39</sup> Euthyroidism is achieved in 25% of the time required by sodium levothyroxine. However, the risk of aggravating coronary artery disease is greater<sup>36</sup> because of rapid

absorption, a comparatively short half-life, and high biological activity. In situations requiring a rapid onset or dissipation of thyroid hormone action, therapy with triiodothyronine is appropriate (examples include T3 suppression testing and possibly myxedema coma). Its use in the routine treatment of hypothyroidism is not recommended. The usual replacement dose is 25 to 75 µg per day, given in divided doses to minimize rapid fluctuations in serum T3 levels. T4 serum concentrations during replacement therapy are predictably low or undetectable.

### **DRUG THERAPY OF SPECIFIC HYPOTHYROID STATES**

#### *Myxedema Coma*

Hypothyroid patients, usually elderly with chronic untreated myxedema of any cause, may rarely develop a profound deterioration of consciousness characterized by seizures, hypoventilation, hypothermia, coma, and eventual death. In most instances a precipitating event can be identified. Examples are cold exposure, trauma, infection, gastrointestinal bleeding, sedative or anesthetic administration, vascular occlusion, or the typical metabolic derangements accompanying severe hypothyroidism, namely hypoxia, hypoventilation, hyponatremia, and hypoglycemia.<sup>40</sup> The mortality of treated patients exceeds 50%. Best results are achieved when the severely hypothyroid state is rapidly reversed.<sup>41</sup>

Therapeutic approaches include correction to the hypometabolic state and associated biochemical abnormalities, treatment of intercurrent illness or infection, and institution of appropriate supportive measures. The latter include assisted ventilation, and management of seizures, hypotension, congestive heart failure, and co-existing or induced (by thyroid hormone therapy) arrhythmias. Intensive monitoring is mandatory. Hypothermia is best treated by protecting against further heat loss with a blanket, not active warming. Occasionally, intestinal ileus or bladder atony may lead to megacolon or urinary retention.<sup>41,42</sup>

Thyroid hormone therapy is instituted as soon as the diagnosis is suspected, although some patients with hypoglycemia, hyponatremia or marked hypercarbia will regain consciousness by correcting the specific biochemical abnormality. The thyroid hormone preparation of choice, its dose, and the route of administration are not well established. Good results have been achieved with sodium levothyroxine, 400 to 500 µg intravenously (IV), followed by 50 µg IV or 100 µg orally each day thereafter.<sup>42,43</sup> Intramuscular and oral routes are less reliable for initial therapy. Alternatively, sodium L-triiodothyronine (liothyronine), which is well absorbed from the intestine even in coma, is effective in doses of 12.5 µg via nasogastric tube,<sup>44</sup> repeated every 6 to 12 hours. IV triiodothyronine,

10 to 50  $\mu\text{g}$  every 6 to 12 hours is also effective,<sup>45</sup> but is not routinely used since parenteral preparations are available only upon request from the manufacturer. (However, a parenteral solution may be prepared locally by dissolving triiodothyronine powder in 0.1 N sodium hydroxide and mixing this with an albumin solution). Higher IV doses are associated with cardiac arrhythmias,<sup>46</sup> and intramuscular doses are poorly absorbed.<sup>47</sup> The major theoretical advantage of triiodothyronine over thyroxine in myxedema coma is the more rapid onset of metabolic effect. However, thyroxine reportedly produces effects within six hours of the initial dose, and conversion of T<sub>4</sub> to T<sub>3</sub> occurs within the first 24 hours following IV administration to hypothyroid subjects.<sup>48</sup>

Hydrocortisone (or its equivalent), 200 to 300 mg IV, is routinely given on the first day because adrenocortical function may be abnormal for reasons such as hypopituitarism accompanying secondary hypothyroid states,<sup>49</sup> a reversible form of hypothalamic-pituitary dysfunction that may occur in all types of hypothyroidism,<sup>48</sup> and, rarely, coexistent primary adrenal insufficiency with autoimmune hypothyroidism.<sup>50</sup> Steroids should be maintained throughout the treatment period or until further study establishes they are no longer necessary. Fluids should be given sparingly because total body sodium is generally above normal and inappropriate antidiuretic hormone secretion may be present.<sup>51,52</sup> Free water clearance may be impaired, and a dilute fluid load may further impair consciousness by aggravating hyponatremia. Small volumes of hypertonic saline are occasionally required to correct severe hyponatremia. Hypoglycemia is corrected with bolus injections of 25 to 50% dextrose to avoid excess fluid. Concurrently administered antibiotics, cardiac glycosides, antiarrhythmic agents, vasopressors, anticonvulsants, and other agents should be given in reduced dosage since drug clearance in general may be impaired. In particular, patients receiving thyroid hormone may be excessively sensitive to vasopressors;<sup>46</sup> they should be used to treat hypotension only in extreme circumstances.

Successful treatment of myxedema coma results in noticeable improvement in the first day, continuing thereafter for weeks to months. Many patients will have suffered irreversible brain damage at the outset of therapy, making complete recovery unlikely.<sup>40</sup>

### *Neonatal Hypothyroidism*

Prompt institution of lifelong thyroid hormone replacement before three months of age in hypothyroid infants significantly improves intelligence quotients.<sup>53</sup> A major problem has been early clinical recognition, but recently the technique of T<sub>4</sub> and TSH immunoassay with very small blood samples was developed for rapid screening of newborns for clinically occult hypothyroidism.<sup>54</sup> Infants sus-

pected of have a form of congenital hypothyroidism<sup>55</sup> or born of mothers given thionamides for hyperthyroidism should have thyroid hormone measurements on cord blood using the standard radioimmunoassay techniques.

Sodium levothyroxine, 10 to 12  $\mu\text{g}/\text{kg}$  daily to a maximum of 0.1 mg daily, is an appropriate starting dose for children less than one year of age. Lower initial doses (25  $\mu\text{g}$ ) with stepwise increments (25  $\mu\text{g}$  per week) offer no advantage (except possibly when congenital heart disease coexists) and theoretically worsen the prognosis by prolonging the hypothyroid state.<sup>56</sup> Thereafter, dose adjustments are based on the measurement of TSH and thyroid hormones.

Successful intrauterine treatment of a hypothyroid fetus by transuterine injection into the fetal buttock has been reported.<sup>57</sup> Experience with this approach is limited, but should be considered when the mother has been inadvertently treated with radioactive iodine.

### *Primary Hypothyroidism*

*Following treatment of hyperthyroidism.* Radioactive iodine or surgical treatment of hyperthyroidism account for a large number of adult cases of hypothyroidism. The early rate of development of hypothyroidism (first year) is less when low doses of radioactive iodine (or larger postsurgical thyroid remnants) are used compared to higher dosage regimens. After the first year there is a 3-5% incidence of hypothyroidism that is independent of dose. All patients who have received radioactive iodine or surgery are therefore at high risk of developing hypothyroidism and require indefinite reassessment of thyroid function at frequent intervals.<sup>58-61</sup>

Selection of candidates for replacement therapy and the appropriate interval of follow-up are controversial issues. Preliminary studies of T<sub>3</sub>, T<sub>4</sub>, and TSH serum levels after thyroid ablation allow certain management recommendations to be made although it should be recognized that this approach may change as further studies delineate more clearly the natural history of post-ablative hypothyroidism. A normal TSH, T<sub>3</sub>, and T<sub>4</sub> suggest adequate thyroid function, and no treatment is required. However, many patients have elevated TSH levels; some of these have low T<sub>4</sub> (hypothyroid), while others have normal T<sub>4</sub> levels (compensated hypothyroid). Thyroid replacement is recommended only in the hypothyroid group,<sup>62</sup> although the compensated group is clearly at risk of developing subsequent hypothyroidism<sup>56</sup> and might conceivably benefit by early replacement. Patients with normal thyroid hormone levels after<sup>131</sup>I and perhaps also after surgery may be followed in two groups — annual follow-up for those with raised serum TSH, and biennial or triennial follow-up for those with normal serum TSH.<sup>63</sup> Replacement doses of thyroid hormone for post-ablative hypothyroidism may be lower than usual because of continued non-

TABLE 2

CAUSES OF THYROID INSUFFICIENCY	
Classification	Special Features
I. PRIMARY	
1. Post-ablative	Follows radioactive iodine or surgery for thyrotoxicosis
2. Autoimmune (chronic thyroiditis, idiopathic hypothyroidism, "burnt out" Graves' disease)	Thyroid antibodies positive in most. Pernicious anemia and other primary endocrine deficiencies may coexist.
3. Thyroid dysgenesis	Most common cause of neonatal hypothyroidism
4. Inherited intrathyroidal defects	Goiter, family history
5. Subacute thyroiditis	Transient phase usually preceded by sore neck and thyrotoxicosis with low <sup>131</sup> I uptake; hormone replacement, if needed, is temporary.
6. Drugs (iodides, lithium, thionamides)	Coexistent thyroiditis (autoimmune), prior ablative therapy, recent history of drug administration
7. Head and neck irradiation	History of treatment for head or neck neoplasm (may be primary, secondary or tertiary)
8. Neoplasia	Primary or metastatic tumor (very rare)
II. SECONDARY	Associated tropic hormone deficiencies; low TSH and poor TSH response to TRH; requires thorough evaluation for underlying cause of pituitary failure
III. TERTIARY	Same as secondary except TSH response to TRH may be preserved but delayed

suppressible function in the remaining thyroid remnant.

Transient hypothyroidism with subsequent recovery occasionally occurs in the immediate post-ablative period, possibly due to prolonged oversuppression of pituitary thyrotropic function.<sup>64</sup> Thyroid hormone may be needed for a short period, but if the requirement persists beyond 4 to 6 months it will likely be permanent.

*Autoimmune thyroiditis – idiopathic hypothyroidism.* Non-ablative primary thyroid failure in children and adults most often results from chronic autoimmune thyroiditis and may be differentiated from other causes (see Table 2) by the presence of thyroid antibodies. Primary adrenal insufficiency, which occurs in less than 2% of patients, should be corrected before thyroid hormone is given in order to prevent adrenal crisis.<sup>65</sup> Vitamin B12 deficiency, secondary to deficiency of intrinsic factor, occurs with high frequency (10 to 15%).<sup>66</sup> Accordingly, blood counts (with red cell indices) or serum vitamin B12 levels should be determined at intervals. Other endocrine deficiencies (hypogonadism, hypoparathyroidism)<sup>65</sup> occur less often but may be important in children when thyroid hormone therapy fails to correct the abnormalities of growth and sex maturation.

Subclinical hypothyroidism, detectable only by an elevated TSH level, but apparently normal thyroid hormone indices, may antedate by many years the appearance of clinical hypothyroidism.<sup>67</sup> It remains to be determined whether early treatment of subclinical hypothyroidism has a beneficial effect in retarding the development of coronary artery disease.<sup>68</sup>

*Other forms of primary hypothyroidism.* Patients with chronic thyroiditis, previous radioiodine therapy, or thyroidectomy are particularly susceptible to the effects of drugs that impair thyroid hormone synthesis and release. Iodides,<sup>69</sup> contained in cough preparations, vitamin pills and radiographic dyes, and lithium carbonate,<sup>70,71</sup> used to treat bipo-

lar affective disorders, may cause hypothyroidism. Patients become euthyroid again several weeks after stopping the offending agent. Subacute thyroiditis may pass through a stage of decreased thyroid reserve lasting a few weeks to several months. Inborn errors of metabolism, mentioned above, are reviewed elsewhere.<sup>55</sup> Treatment of tumors by head and neck irradiation<sup>72</sup> may cause primary, secondary, or tertiary hypothyroidism due to thyroid, pituitary or hypothalamic damage. Iodine deficiency leading to hypothyroidism is almost nonexistent in the United States.

#### *Secondary and Tertiary Hypothyroidism*

Pituitary or hypothalamic disease causing hypothyroidism is readily diagnosed when both T4 and TSH levels are low. An absent TSH response to TRH suggests secondary hypothyroidism; a normal response suggests tertiary hypothyroidism. However, the TRH test is not entirely satisfactory in separating pituitary from hypothalamic disease.<sup>9</sup> TSH deficiency may occur alone (idiopathic thyrotropin deficiency) but most often is accompanied by deficiencies of other pituitary tropic hormones resulting from tumors, pituitary necrosis, hypophysectomy, irradiation, or granulomas. The distinction from primary hypothyroidism is of great importance because latent pituitary ACTH deficiency may be unmasked by thyroid hormone therapy and result in adrenal crisis. Hydrocortisone, 25 to 50 mg daily, or its equivalent, should be given before thyroid hormone supplements when this need has been established. The treatment of gonadotropic and growth hormone deficiencies are discussed elsewhere.<sup>73,74</sup>

#### MANAGEMENT OF PATIENTS ALREADY RECEIVING THYROID HORMONE

Thyroid hormones are used in many other diagnostic and clinical settings.<sup>75</sup> Their use for treating nonspecific symptoms suggesting hypothyroidism without adequate laboratory confirmation is seldom

justified, although rare situations exist where the diagnosis remains in doubt. Here a short supervised trial of hormone replacement may be indicated.

Patients receiving thyroid medication over many years for unclear reasons are frequently encountered. The need for continued therapy may be in question. This problem may be approached in one of two ways. First, the TSH stimulation test may be applied. The 24-hour uptake of radioactive iodine measured before and following TSH, 10 units intramuscularly daily for 2 to 3 days, should significantly increase if the thyroid gland is normal. A disadvantage of this method is that more than 75% of patients with mild hypothyroidism may respond normally.<sup>67</sup> The second approach is to withdraw the thyroid medication and measure the plasma TSH and thyroid hormone levels in 6 weeks. Prolonged exogenous thyroid hormone administration results in impaired TSH responsiveness and subnormal thyroid hormone levels, which, however, return to normal by 5 weeks.<sup>76,77</sup>

### SICK EUTHYROID OR LOW T3 SYNDROME

Patients that have had surgery or have a variety of acute and chronic nonthyroidal diseases may have low serum T3 levels with no clear clinical signs of thyroid insufficiency. Associated abnormalities include low normal or normal total serum T4, and raised free T4.<sup>78</sup> The TSH and TSH response to TRH may be slightly elevated although generally not as high as in primary hypothyroidism.<sup>79</sup> The low T3 results from impaired peripheral conversion of T4 to T3, together with increased conversion of T4 to "reverse T3," a metabolically inactive form of T3. This condition is important only inasmuch as it might lead to misdiagnosis of hypothyroidism.

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# PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

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*The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.*

*The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.*

## **The Advantages**

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy—and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

## **The Disadvantages**

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information

is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

## **The Solution**

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

**PMA**

THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION  
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## Maine Department of Human Services

# Legionnaires' Disease: Preliminary Report on Its Diagnosis, Etiology, Pathology, and Therapy

WILLIAM NERSESIAN, M.D.\*

Although there is still much to be learned, enough information has been gathered about the Legionnaires' disease and its etiologic agent that a preliminary composite of the salient features of the disease, its course, and approach to the diagnosis and therapy can be formulated. Evidence strongly suggests that the same bacterium which caused the outbreak of pneumonia in Philadelphia in 1976 also caused outbreaks in the District of Columbia in 1965, in Pontiac, Michigan in 1968, and in Philadelphia in 1974. Between August 1976 and September 1, 1977, over 20 sporadic cases of pneumonia associated with the same bacterium have been identified from 11 States. Of these sporadic cases, the diagnosis in two was first made by isolating the organism on bacteriologic medium; in a third case, the isolation of the agent was made by inoculating post-mortem lung tissue into a guinea pig; the remaining cases were diagnosed by demonstrating significant rises in titer in paired sera. Clearly, the disease is neither localized nor new.

### *Clinical Findings:*

Legionnaires' disease begins 2 to 10 days after exposure. In the typical case, the earliest symptoms are malaise, muscle aches, and a slight headache. Within less than a day, there is a rapidly rising fever associated with chills. A nonproductive cough is common early, often with the onset of initial symptoms. Abdominal pain and gastrointestinal symptoms also occur in many of the patients. Temperatures commonly reach 102 to 105 F (39-41 C). When first examined by a physician, most patients have been found to have rales without evidence of consolidation. The rest of the findings on physical examination are usually normal, although some patients have been obtunded. Initial laboratory findings often include a leukocytosis (in 60%) with a left shift, 3+ proteinuria or greater (in 20%), erythro-

cyte sedimentation rate greater than 80 mm per hour (in 33%), and, in a significant minority, hyponatremia, mild azotemia, and elevation of the serum glutamic oxaloacetic transaminase (SGOT) and alkaline phosphatase. Chest x-rays show patchy, interstitial infiltrates or areas of consolidation which progress to more widespread consolidation. Effusions, when present, are usually minimal.

Illness usually progresses over the 2 to 3 days after hospitalization. Cough commonly becomes productive, but the sputum is rarely purulent. Approximately 15% of the patients die, either of shock or respiratory failure. Upper and lower gastrointestinal bleeding is not uncommon, but may be related to the stress of illness. Renal failure has been seen in several patients. In those who recover, the radiographic evidence of improvement lags a few days behind clinical resolution.

### *Chemotherapy:*

No randomized trial of antibiotic therapy has been performed. Of the drugs used, cephalothin has been associated with a relatively high case-fatality ratio and erythromycin and tetracycline, with relatively low case-fatality ratios. These associations with case-fatality ratios, however, may be as much a reflection of the physician's assessment of the severity of illness as they are indications of the efficacy of drug treatment. Agar dilution susceptibility testing has shown the organism to be "susceptible" or "moderately susceptible" to a large number and a wide variety of antibiotics. In general, erythromycin, a number of penicillins, cephalosporins, aminoglycosides, chloramphenicol, rifampicin, and sulfamethoxazole-trimethoprim produce *in vitro* results in the "susceptible range"; tetracycline and methicillin minimum inhibitory concentrations (MIC) were borderline, and vancomycin MIC suggested resistance. There *in vitro* interpretations do not always correlate with *in vivo* response. Tests in embryonated eggs showed rifampin, gentamicin,

\*Maine Bureau of Health

streptomycin, and erythromycin to be most effective in that order. Erythromycin has been effective against experimental infection in guinea pigs. Similar studies with other antibiotics are under way. At present, it is impossible to say what is the best antibiotic to use in treating patients with Legionnaires' disease, but erythromycin appears to be a promising agent.

#### *Pathology:*

In fatal human cases, the pneumonia caused by the Legionnaires' disease organism has been of the lobar type. Since we have not had the opportunity to examine lung biopsy tissues from patients surviving the disease, we cannot characterize early lesions or milder manifestations of the disease. In paraffin sections the organism stains poorly with tissue gram stains (i.e. Brown-Brenn and Brown-Hopps stains) and the giemsa stain. It does not stain at all with hematoxylin and eosin, acid fast, gimenez, and methenamine silver strains. In our experience the dieterle silver impregnation procedure consistently demonstrates the organism in paraffin-embedded sections. The largest number of organisms is associated with intraalveolar proteinaceous debris and infiltrates of polymorphonuclear neutrophils and macrophages.

#### *Isolation and Identification of the Etiologic Agent:*

The initial isolations of the bacterium of Legionnaires' disease were made in guinea pigs inoculated with lung tissues obtained postmortem from 4 patients. The guinea pigs developed a febrile illness characterized by watery eyes and prostration 1 to 2 days after inoculation. Moribund animals were sacrificed 3 to 6 days after onset of fever, and specimens from the spleen, liver, and lungs were inoculated into 7-day-old embryonated hens' eggs. The eggs died 4 to 6 days after inoculation, and smears of yolk sacs stained by the gimenez method showed bacilli 0.3-0.4  $\mu\text{m}$  in width and of various lengths. The etiologic role of the bacterium was established by indirect fluorescent antibody (IFA) tests with appropriate sera from patients with Legionnaires' disease.

Primary isolation on bacteriologic media of the bacterium considered to be the etiologic agent has been obtained in five reported instances. In three cases — two Legionnaires' cases and one sporadic case this year — lung tissue obtained postmortem was successfully cultured on an agar medium. In

two cases, the organism was isolated from pleural fluid obtained before the patients' death, both of whom were taking corticosteroids for an underlying autoimmune disease. There is no reported experience with attempts to isolate the organism from sputum. However, should sputum, transtracheal aspirations, bronchial washings, or endotracheal aspirations be submitted to the laboratory with the request that isolation of the Legionnaires' organism be attempted, the microbiologist should use Mueller-Hinton or GC agar (or their equivalents) containing 1% hemoglobin and 2% enrichment (Isovitalex\* — BBL — or its equivalent). Although hemoglobin is preferred, 5% Fildes enrichment (peptic digest of sheep blood) can be substituted for hemoglobin. Growth will also occur in Mueller-Hinton broth supplemented with Fildes enrichment (3%-4%) and Isovitalex (2%). The final pH of these media should be adjusted to pH 6.9 to 7.0. *The Maine state laboratory does not attempt to culture the organism at this time.* We can arrange for tissue specimens to be sent to Atlanta for culture; however, this should be done only in cases of near-fatal or fatal illness.

Although isolation of the bacterium has been achieved, *the most practical method of documenting Legionnaires' disease in living patients is by serologic testing with immunofluorescent antibody.* Samples of acute and convalescent sera may be submitted to the state lab and these will be forwarded to Atlanta for testing. The Convalescent serum must be drawn *at least 3 weeks after the acute specimen* or else a false-negative may occur. Since laboratory confirmation of Legionnaires' disease occurs long after the patient has either convalesced or died, *the attending physician should not wait for confirmation to treat with antibiotics.*

#### *Isolation procedures:*

There is currently no evidence that Legionnaires' disease spreads from person-to-person, and hospital staff exposed to patients have *not* contracted the illness. However, because mode of transmission is still unknown, and because some patients suspected of having Legionnaires' disease may actually have a viral or mycoplasma pneumonia, standard respiratory isolation would seem prudent.

(The majority of this report taken from a CDC memorandum to state epidemiologists, dated 9/1/77.)

# County Society Notes

## Penobscot

The annual meeting of the Penobscot County Medical Society was held on May 17, 1977 at the Stable Inn in Brewer, Maine.

The meeting was opened by the President, Dr. John A. Woodcock, and the minutes of both the March and April meetings were discussed and approved. The detailed minutes of the March meeting discussing Mr. Cragin's presentation were read in their entirety as a sample of the type of expanded minutes planned for next year which is to serve as a Newsletter. The reinstitution of the Newsletter had been approved at our January meeting. It was felt by the Executive Committee that an expanded and more detailed minutes that could be circulated among the membership would serve as a Newsletter.

Under further old business, Dr. Merriam reported to us on his activities as Chairman of the Liaison Committee with the Press. It was felt that this committee did indeed serve a useful function during the past year in ironing out some areas of misunderstanding between the medical community and the Press. A letter to the Committee on Health and Institutional Services stating the County Society's support for LD 453 and LD 991, smoking restrictive bills, was read. And finally it was noted that at the recent hearing regarding the proposed closing of Bangor Mental Health Institute, the opposing points of view from this area, as presented by Drs. Ordway, Kellogg and Tamm, were favorably received.

Under new business, the applications for membership from Dr. Robert D. Tomlinson and Dr. Donald E. Factor were presented and unanimously accepted. The application from Dr. Denis F. J. Halmagyi of Lincoln, Maine was incomplete in its lacking two letters of reference as required by our bylaws and this is to be requested for presentation at our next meeting.

The proceedings of the interim meeting of the House of Delegates of March 27, 1977 was then discussed; in particular, the resolutions that are to be voted upon at the annual meeting in Rockport in June were presented and considered by the membership for instructions to our delegates to this meeting in regard to these resolutions. The resolution regarding extension of past presidents' terms on the Executive Committee to a maximum of three years was unanimously supported. The resolution from the Kennebec County Medical Association regarding support and assistance to Medical Care Development, Inc., was felt to be somewhat unclear in the mechanism of the aid Maine Medical Association is supposed to give, as well as the mechanism for this aid. Medical Care Development, Inc. was explained and clarified for us by Dr. Charles D. McEvoy, Jr. It was the consensus of the membership that the delegates attend the Reference Committee meetings in Rockport prior to the formal voting session so that they may become more familiar with this resolution. The resolution to move the Maine Medical Association headquarters to Augusta, Maine no later than January 1979 was supported in part; the membership felt that when a move is to be made that Augusta should be the site; however, they felt placing a date for the move was too restrictive. And finally, the resolution to amend the bylaws in Chapter 4, Section 10 was considered inappropriate and it was felt this resolution should not be supported by our Society.

Finally, the Chairman of the Nominating Committee, Dr. Thornton W. Merriam, Jr. presented the new slate of officers and delegates for the year 1977-78. This was unanimously approved. These officers are:

President: Dr. Philip G. Hunter, Bangor

President-elect: Dr. David S. Beebe, Bangor

Secretary: Dr. H. Clement Jurgeleit, Bangor

Treasurer: Dr. A. Marshall Smith, Bangor

Executive Council (Term — 3 years): Dr. Francis I. Kittredge, Bangor

Delegates to the M.M.A. House of Delegates: Drs. James R. Curtis, Jack N. Meltzer, Leonardo Leonidas, Robert P. Andrews and Francis I. Kittredge, all of Bangor; Dr. A. Dewey Richards, Orono and Dr. John J. Pearson, Old Town.

Alternates: Drs. G. Douglass Timms, John F. Adams, Jr., Parker F. Harris, Richard L. Field, Sidney Chason, Don L. Maunz and R. Russell Lang, all of Bangor.

There being no further business, the meeting was adjourned at 10:00 p.m.

H. CLEMENT JURGELEIT, M.D., *Secretary*

## Knox

The Knox County Medical Society met at the Sail Loft Restaurant in Rockport on September 13, 1977.

The secretary called the members' attention to communications he had received. The Maine Medical Association was requesting an updated list of affiliate and retired memberships. None of our members qualified to be added on this list at this time.

The secretary also reminded the members of the notification that Blue Cross and Blue Shield of Massachusetts will be handling the Medicare Program.

Dr. John W. Wickenden discussed the possibility of a captive insurance company for Malpractice Insurance in Maine to provide better security at lower rates. He said the new President of the M.M.A. is Dr. Douglas R. Hill. He also announced that a malpractice bill had been passed by the legislature and that Dr. Francis I. Kittredge will soon be reporting to delegates on the impact of the bill.

Dr. Jack D. McCue addressed the membership on "Review of Coronary Risk Factors."

There being no further business, the meeting was adjourned.

JACK D. MCCUE, M.D., *Secretary*

## Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges, Wiscasset, Maine on September 20, 1977.

There were twenty-six members and guests present.

The meeting was called to order, after dinner, at 8:25 p.m., by the President, Dr. Anthony J. Horstman. The minutes of the May meeting were read by the Secretary and accepted as read.

Dr. Horstman introduced Dr. Douglas Long, the new family physician from Boothbay Harbor and then introduced Dr. Douglas Hill, of South Portland, President of the Maine Medical Association.

Dr. Hill spoke on activities of the Executive Committee of the M.M.A.: exploration of methods such as a physician-directed insurer to help the professional liability insurance problem, Medicaid fees directed by the Department of Human Services, the probable exclusion of physicians from the tentacles of Certificate of Need, the hiring of a director of public relations, the creation of an Issues Committee for M.M.A., the installation of an Assistant to the Executive Director, and other items. He announced the imminent arrival of a questionnaire about malpractice and urged all members to respond.

Dr. Schall expanded on the budget voted at the June Annual Meeting and on the projected removal of the M.M.A. office from Brunswick to Augusta. Dr. Leck then mentioned the work of the *ad hoc* committee studying professional liability insurance, and again urged cooperation with the mail survey.

The Board of Censors recommended the acceptance to active membership of Dr. John F. McGeough of South Harpswell and Dr. Douglas G. Long of Boothbay Harbor. Dr. Currier McEwen of South Harpswell was accepted into honorary membership. The vote for acceptance was unanimous.

Dr. Cote was then introduced by Dr. Avantage and spoke on cervical colposcopy.

GEORGE W. BOSTWICK, M.D., *Secretary*

## Washington

A regular meeting of the Washington County Medical Society was held on October 6, 1977, in the Staff Lounge, at the Down

East Community Hospital, with eight members and guests present.

I. *Minutes of last meeting* read, with a change.

a. Voted that any matters affecting Washington County Health Plan and Certificate of Need of Legislation would require a vote of all members of the Society by ballot.

II. *New business:*

a. The following applications reviewed and accepted as new members of the Washington County Medical Society: Drs. Carl K. Aselton, Milbridge, John W. Peterson, Calais and Eric M. Burke, Machias.

b. Considerable discussion of the ten percent reduction in Medicaid fee schedule and of the suit that the Maine Medical Association and others are making to oppose this change. No definitive action.

c. The following members elected to the Maine Medical Association House of Delegates: Delegate — Dr. Robert G. MacBride, Lubec and Alternate — Dr. Donald G. Robertson, Milbridge.

d. Discussion of the transfer of Medicare Union Mutual to

Massachusetts Blue Shield. The Society voted that a letter of appreciation be sent to Union Mutual and thanks for their years of service and for their successful attempts to simplify and improve which, to the doctors, seemed to be a very complex problem.

e. Discussion of Washington County Health Plan, principally by Dr. G. Bernard Shaw of Machias, Maine, who felt that the doctors should have some input regarding the new contract. It was suggested and approved, that Dr. Robert G. MacBride the only medical doctor representative on the WCHP board, be asked to speak at the next meeting in regard to the WCHP.

III. *Old business:*

a. Discussion of complaint by Erland Doten. It was felt that this was entirely a Calais Regional Hospital problem.

b. It was also voted that the Society take no further action on the Sabry Mason case, and at present, consider this case closed.

IV. It was voted to hold the next meeting of the Washington County Medical Society on November 17, 1977 at the Calais Regional Hospital.

KARL V. LARSON, M.D., *Secretary*

### **The Third Annual Midwinter Virgin Islands Clinical Conference**

The third Mid-Winter Virgin Islands Clinical Conference will be held in St. Thomas, January 26, 27, 28, 1978 by the U.S. Virgin Islands Medical Society in association with The Faculty of The Johns Hopkins University School of Medicine.

This program is acceptable for 14 credit hours in Category I for the Physician's Recognition Award of the A.M.A., and will include lectures and seminars of interest to the physician in General Practice, Internal Medicine, General Surgery, OB-Gyn and Pediatrics.

For further information, write to: Peter A. Curreri, M.D., III Annual Clinical Conference, Box 39, Red Hook, St. Thomas, V. I. 00801.

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March 1977



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A	Allergy (sub-specialty of Internal Medicine)	OPH	Ophthalmology
ANES	Anesthesiology	ORS	Orthopedic Surgery
AM	Aerospace Medicine (special field of Preventive Medicine)	OTO	Otolaryngology
CD	Cardiovascular Disease (sub-specialty of Internal Medicine)	PATH	Pathology
CHP	Child Psychiatry (sub-specialty of Psychiatry)	PD	Pediatrics
CRS	Colon and Rectal Surgery	PDA	Pediatric Allergy (sub-specialty of Pediatrics)
D	Dermatology	PDC	Pediatric Cardiology (sub-specialty of Pediatrics)
DR	Diagnostic Roentgenology (special field of Radiology)	PMR	Physical Medicine and Rehabilitation
FOP	Forensic Pathology (special field of Pathology)	PS	Plastic Surgery
FP	Family Practice	P	Psychiatry
GE	Gastroenterology (sub-specialty of Internal Medicine)	PH	Public Health (special field of Preventive Medicine)
GPM	General Preventive Medicine (special field of Preventive Medicine)	PUD	Pulmonary Diseases (sub-specialty of Internal Medicine)
GS	General Surgery	R	Radiology
IM	Internal Medicine	TR	Therapeutic Radiology (special field of Radiology)
NS	Neurological Surgery	TS	Thoracic Surgery
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 St. George 0485  
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 Main St., Waldoboro 0457  
 121 Main St., Thomaston 0486  
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## An Alphabetical List of the Members of the Maine Medical Association

The figures in parentheses refer to County Societies as follows: (1) Androscoggin, (2) Aroostook, (3) Cumberland, (4) Franklin, (5) Hancock, (6) Kennebec, (7) Knox, (8) Lincoln-Sagadahoc, (9) Oxford, (10) Penobscot, (11) Piscataquis, (12) Somerset, (13) Waldo, (14) Washington, (15) York.

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 Adams, Payson S., Jr., Mercy Hospital, Portland 04101 (3)  
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 Agan, Robert W., 144 State St., Portland 04101 (3)  
 Akar, Hamdi, 37 Oak St., Bath 04530 (8)  
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 Andalkar, Ratnakar R., 163 Main St., Norway 04268 (9)  
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 Anderson, John B., Dudley Coe Inf., Bowdoin College, Brunswick 04011 (3)  
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 Andrews, Anneliese M., Maine Medical Ctr., Portland 04102 (3)  
 Andrews, Edward C., Jr., Maine Medical Ctr., Portland 04102 (3)  
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 Batosingh, Edward, 47 Hardy St., Presque Isle 04769 (2)  
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 Beegel, Paul M., 10 High St., Lewiston 04240 (1)  
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 Naum, Bogdan G., 152 Main St., Madison 04950 (12)  
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 Nematollahi, Heidar, 10 High St., Lewiston 04240 (1)  
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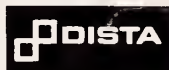
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**Usage in Pregnancy:** Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

**Precautions:** If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

**Side Effects:** Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.



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**Usage in Pregnancy:** Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

**Precautions:** In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psycho-

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tropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relation-

ship has not been established clinically.

**Adverse Reactions:** Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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